# Treatment of lower urinary tract infections in an era of increased antimicrobial resistance

**Ian Mifsud** B.Pharm (Hons), MSc. Env. Mgt . PG Cert Clinical Pharmacy

Senior Pharmacist – Rehabilitation Hospital Karen Grech
**Email:** ian.a.mifsud@gov.mt

**Educational aims**

- To provide an overview of the OTC preparations available for the prophylaxis and treatment of acute uncomplicated cystitis
- To highlight the reasons as to why nitrofurantoin and co-amoxiclav are the antimicrobials of choice in the empirical treatment of lower urinary tract infections
- To illustrate the limitations of nitrofurantoin treatment
- To demonstrate why fluoroquinolones are not the ideal choice in the treatment of lower urinary tract infections

**Key words**
lower urinary tract infection, bacteruria, nitrofurantoin, co-amoxiclav, ESBL positive pathogens

**Abstract**

**The antibiotic arsenal for treatment of lower urinary tract infection is becoming increasingly limited. Co-trimoxazole has been lost in the empirical treatment of urinary tract infection. Other agents particularly fluoroquinolones are becoming ineffective. Locally, the empirical treatment of such infection focuses on two antibiotics – nitrofurantoin and co-amoxiclav. Carbapenems are increasingly being prescribed due to the emergence of ESBL (extended spectrum beta lactamase) positive pathogens.**

## Introduction

Acute cystitis is a condition for which the community pharmacist is likely to come across on a regular basis. This condition is normally characterised by dysuria, urgency and/or frequency. However such classical symptoms may not be apparent in the elderly who may instead present with confusion or incontinence. The presence of symptoms such as fever, chills or back pain are indicative of bacteraemia as well as kidney involvement. Referral is also always indicated in the latter cases, as is also for all cases of lower urinary tract infections in men, children and pregnant women. The community pharmacist should also be aware that there are other causes for dysuria, such as sexually transmitted diseases.[1] Suspicion of such infections should always be referred for appropriate treatment.

Bacteriuria does not always present with symptoms. Asymptomatic bacteriuria is a common occurrence in the elderly as well as catheterised patients and does not merit treatment. Treatment of asymptomatic conditions in the elderly does not decrease the frequency of symptomatic infection but increases the risks of adverse drug reaction and promotes urinary tract infection with resistant organisms.[2] In cases of long-term indwelling catheters there is conflicting evidence on whether use of antibiotics in asymptomatic patients reduces the frequency of symptomatic episodes but repeated use of antibiotics increases the risk of colonisation by resistant bacteria.[2]

## OTC preparations for the treatment and prophylaxis of cystitis

Women presenting with symptoms of cystitis and who do not need to be referred should be advised to maintain adequate hydration. They can also be offered alkalinising agents for a couple of days, although the evidence base for this recommendation is limited. The use of alkalinising agents is not recommended in individuals with hypertension or heart failure as these preparations contain a high sodium or potassium content. Caution should be exercised when recommending potassium alkalinising preparations to patients on medication that predispose to hyperkalaemia eg ACE inhibitors and potassium sparing diuretics. Alkalinising agents should not be used in patients prescribed nitrofurantoin, as this drug requires an acidic urine pH to be effective.[2]

Other OTC preparations that are commonly associated with cystitis are cranberry products. Evidence to support the use of these products for treatment of cystitis is lacking. The recommendation of such products should be restricted to the prevention of such infections in premenopausal women with a history of recurrent infections.[2] Evidence is also lacking for the effectiveness of cranberry products for their prophylactic effect in the elderly and catheterised patients. The optimal dose has not been established but giving a minimum of 36 mg/day proanthocyanindin A (the active compound), is favoured.[3] It might be appropriate to recommend cranberry capsules as an alternative to the juice as a solid dosage form may be more convenient to the patient. The use of cranberry products is not generally recommended in patients on warfarin as interactions resulting in an increase the INR can occur.[4]

Cystitis originates primarily from pathogens in the bowel flora. By far the most commonly implicated organism is *Escherichia coli*. Traditionally co-trimoxazole was prescribed for cystitis, however, over the past decades local resistance has developed to the degree that this antibiotic is no longer indicated in the empirical treatment of urinary tract infection. From local clinical practice this antibiotic retains its high efficacy against MRSA.

**Empirical treatment in the community**

Current local community guidelines indicate nitrofurantoin and co-amoxiclav as the drugs of choice.[5] The exclusive indication of nitrofurantoin is cystitis. This drug lacks tissue penetration, only reaching therapeutic concentrations within urine. For this indication nitrofurantoin remains the most efficacious oral agents with little acquired resistance over the 60 year period in clinical use. The bactericidal potency of nitrofurantoin is affected by pH, its potency reducing rapidly as urine becomes more alkaline. For this reason nitrofurantoin should not be prescribed for infections characterised with a urine pH greater than 7. A high urinary pH may also be indicative of a pathogen that produces urease enzymes, such a *Proteus* or *Serratia* which are intrinsically resistant to nitrofurantoin.[6]

Nitrofurantoin has various mechanism of action, being bactericidal at concentration normally reached with therapeutic doses. Its spectrum of activity covers both gram positive as well as gram negative organisms including multidrug resistant strains such as MRSA, vancomycin-resistant enterococci and the extended beta lactamase enterobacteriaceae (ESBL positive organisms). One drawback of this drug is that it is not licensed for use in patients with renal impairment defined by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min. This makes the drug of limited use in the elderly. However literature has shown that nitrofurantoin still remains effective in renal impairment and can be used with caution in patients with mild renal impairment.[7,8,9] In such cases the drug is being prescribed off label.

Nitrofurantoin is prescribed on a 6 hourly basis and should be taken with food primarily to improve absorption but also to limit GI side effects such as nausea (a side-effect which is less frequent with the macrocrystalline formulation). In premenopausal woman acute cystitis usually responds to 3 days treatment. In postmenopausal women or women having well-controlled diabetes without urological sequelae may be managed in the same way as for acute uncomplicated cystitis. But a 7-day course is generally recommended since cure rates with short-course therapy are not as high.[10]

Co-amoxiclav is now the alternative to nitrofurantoin for the empirical treatment of cystitis. The higher dose formulations of co-amoxiclav have often been prescribed on a bd basis however the tds regimen is now generally recommended except for specific hepatic and renal considerations.[11] For cystitis the recommended dose being 625mg every 8 hours. Previous to co-amoxiclav, cefuroxime was widely recommended, having a narrower spectrum than co-amoxiclav but still retaining activity against uropathogens. However the extensive overuse of cephalosporins has led certain gram negative pathogens to develop resistance by enzyme activity - ESBL, enzymes that destroy the beta-lactam ring. For this reason the use of cefuroxime within hospitals has been restricted.[12]

**Restricting the use of fluoroquinolones**

The prescription of fluoroquinolones for cystitis should be guided by laboratory results. Resistance to these antibiotics is at a significant level.[13] Limiting the use of fluoroquinolones for when no suitable alternative is available is a strategy that will help mitigate increasing resistance to this class of antibiotics, not only to uropathogens but also to other pathogens including MRSA.[14] When fluoroquinolones are indicated ciprofloxacin is the favoured antibiotic for urinary tract infections, it has good pharmacokinetic properties, the oral formulation being well absorbed as well as being well concentrated within urine. A low dose (250mg bd) will suffice. Furthermore ciprofloxacin is the gold standard in the treatment of infections caused by *P aeruginosa*. In such cases however a higher doses (500mg bd) should be considered as the minimum inhibitory concentration for *P aeruginosa* is higher than for other organisms. A good fluid intake is recommended with the higher doses of ciprofloxacin as cases of crystaluria have been reported especially in alkaline urine. Since ciprofloxacin absorption is inhibited by multivalent metal ions, pharmacists should advice patients not to take this antibiotic with milk or milk products. Patients on calcium supplementation or multivitamin preparation should also be adviced to take their regular medication 4 hours away from their antibiotic. Pharmacists should also be aware that fluoroquinolones may lower the seizure threshold and may trigger seizures thus should be used with extreme caution in patients predisposed to seizures.[15]

**Recurrent infections**

Individuals with recurrent urinary tract infections (defined as three episodes over the past year or two in the past six months) may be considered for a trial of antimicrobial prophylaxis for up to 6 months if symptoms are debilitating.[2,16] Prophylactic antibiotics should be given at night when urine flow is low. Longer term use is however not recommended as this promotes emergence of resistance. Antibiotic prophylaxis is generally not recommended in catheterised patients. However they may be considered if the frequency and intensity of symptoms impinge on the well-being of the individual.[2]

**Empirical treatment in hospitals**

Antibiotic choice for the empiric treatment of lower urinary tract infections in hospital is similar to community guidelines but in an era of increasing antibiotic resistance, routine urine sampling is recommended in symptomatic patients in order to determine the sensitivity of the pathogen.[17] Urinary tract infection is the most common nosocomial infection and hospitalisation

**Key points**

- Nitrofurantoin is the antibiotic of choice for the empirical treatment of cystitis. Co-amoxiclav is now the recommended alternative to nitrofurantoin.
- Alkalinising agents should not be co-prescribed with nitrofurantoin. This may result in therapeutic failure.
- Cranberry products interact with warfarin. The Committee on Safety of Medicine in the UK does not recommend their concomitant use.
- Alkalinising agents should be used with caution in the elderly as such agents can worsen hypertension and heart failure. Patients on medication which predispose to hyperkalaemia should not use potassium containing preparations.
- Cefuroxime is no longer recommended for the treatment of cystitis - Cephalosporins have been implicated as the driving force for resistance in Gram-negative pathogens.
- Second generation quinolones should be avoided in the empirical treatment of cystitis as resistance is at a significant level. The use quinolones promotes resistance not only among uropathogens but also other organisms.
- Asymptomatic bacteriuria is common in certain categories such as the elderly and individuals with long-term indwelling catheters. Such a condition does not merit antimicrobial treatment.

should be considered a risk for infection with ESBL-producing pathogens. An increasing proportion of patients would have acquired such organisms before hospital admission, reflecting the regrettable over-prescribing of antibiotics in the community. Treatment with co-amoxiclav in such cases is likely to fail and these pathogens could also have acquired resistant to quinolones and aminoglycosides. Carbapenems are increasing becoming the only practical alternative treatment available locally. Ertapenem has an advantage over other carbapenems in that it is given on a once daily basis; it also has a narrower spectrum than other carbapenems, it does not cover *Pseudomonas* and *Acinetobacter* species. In Europe it is used off-licence for urinary tract infection, however it is registered for this indication in the US.[18,19] Carbapenems are not available as oral formulations. Patients requiring such antimicrobials have to undergo IV therapy, an invasive procedure which in its own right predisposes to a hospital acquired infection.[20] Some strains of Gram-negative organisms have also developed resistance to carbapenems thus limiting further the choice of antibiotics.

**A risk for urinary tract infections – catheterisation**

Urinary catheterisation is a common procedure in hospital and long-term care facilities. This procedure predisposes the individual to infection.[20] Risk reduction should be considered - the need and duration for catheterisation should be carefully assessed. Alternatives such as suprapubic or condom catheters should be considered as these carry a lower incidence of urinary tract infections. The technique of intermittent catheterisation is also encouraged especially among spinal cord injury patients. Treatment of catheter associated urinary tract infections without kidney involvement is the same as for patients without catheter.[17] Treatment is only indicated in symptomatic patients, who would also merit a catheter change since biofilms tend to develop rapidly along both the inner and outer surface of the catheter lumen creating a barrier to effective penetration by antibiotics and predisposing to resistance. Biofilms are usually initially caused by single species but rapidly become polymicrobic.[21] As a general guideline seven days of antimicrobial treatment for patients with catheter associated-UTI who have prompt resolution of symptoms is recommended, the duration is prolonged to 10–14 days for those with a delayed response.[22]

**Pivmecillinam and Fosfomycin**

Two other antibiotics indicated for urinary tract infection are available but have not been discussed above since, as yet, they are not registered locally. Both of these antibiotics have been listed as first-line agents in both European and American guidelines.[3,23] Pivmecillinam is registered in some Nordic European countries. It is orally bioavailable and has an extended spectrum against gram-negative *Enterobacteriaceae*. Its sole indication is urinary tract infection. Fosfomycin is registered in the USA as well as various European countries. Its favourable characteristics include the convenience of a single-dose regimen for acute uncomplicated cystitis, very good activity against a range of multi-drug resistant organisms including resistant *Enterobacteriaceae* and minimal propensity to induce resistance.[23]

**Conclusion**

Although antimicrobial resistance is an inevitable natural phenomenon, our professional behaviour is crucial in determining the rate and extent to which pathogens develop resistance. The emergence of ESBL-positive pathogens is challenging our practices and constraining the health care professional to rely increasingly on second-line agents such as carbapenems.

Clinical judgement in the choice of antibiotics, when indicated, is pivotal in ensuring therapeutic success while minimising the negative consequences of therapy.

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