TREATMENT OF LOWER URINARY TRACT INFECTION

SUMMARY
- A three day course of trimethoprim 200mg bd is the agent of choice in uncomplicated UTI.
- Routine culture in uncomplicated UTI in women is unnecessary and expensive.
- Pregnancy is the only indication for treating asymptomatic bacteriuria.
- Infections in males and children warrant further investigation.

INTRODUCTION
The urinary tract is the second commonest site of bacterial infection and is a cause of significant morbidity both in terms of the number of people affected and the potential complications.

Urinary tract infections (UTI's) can be classified into complicated or uncomplicated UTI's. An infection is considered to be complicated if it affects pregnant women, children, men or the elderly or if it affects the upper tract. Uncomplicated UTI's involve the lower urinary tract and encompass the syndrome of acute dysuria and frequency in otherwise healthy, non-pregnant women.

Significant bacteriuria is generally regarded as cultured urine that yields a pure growth of organisms of greater than \(10^5\) colony forming units (CFU) per ml. Sometimes a pure growth of \(>10^3\) CFU/ml may be clinically important. The basis of management is the recognition that UTI's have vastly differing significance depending on the patients clinical picture, sex and age.

CAUSATIVE ORGANISMS AND DIAGNOSIS
Most UTI's result from ascent of the organism into the bladder via the urethra. E.Coli is the most commonly isolated organism. Others include Proteus mirabilis and Klebsiella species which may be quite resistant to antimicrobials. Staphylococcus saprophyticus can account for up to 10% of UTI's in sexually active women.

The optimal way of dealing with UTI is to take a mid-stream specimen of urine and then commence an appropriate antibiotic. With the results of cultures and sensitivity and depending on the patients response, treatment can be altered if necessary. In practice, diagnosis is often made on the basis of typical signs and symptoms supported by a positive dipstick urinalysis for nitrites and leucocytes.

UTI'S IN DIFFERENT PATIENT GROUPS
Lower tract symptoms are common in adult females. Approximately one half will have a bacterial cystitis. The differential diagnosis of the others include mainly the urethral syndrome and to a lesser extent, sexually transmitted disease or vaginitis. The urethral syndrome describes the syndrome of frequency and dysuria without bacteriuria. A non-pregnant woman can be managed on the basis of a dipstick urinalysis. If positive, a short course of a best guess antibiotic can be given. Symptoms may fail to resolve initially after treatment but if they persist a urine culture or tests for other causes should be undertaken. Non-pregnant adult females with a negative dipstick and in whom the urethral syndrome is suspected may be advised on the need for a high fluid intake, regular and complete bladder emptying, good local hygiene and alkalinisation of the urine using potassium citrate mixtures.

The only clear indication for treatment of asymptomatic bacteriuria is during pregnancy. Many children with UTI, particularly neonatal males, have congenital structural abnormalities. All children, male and female should be referred for investigation following their first proven UTI. A prophylactic sugar-free antibiotic at low night-time dose should be continued until investigations are complete. If reflux is present prophylaxis needs to be continued until spontaneous resolution, surgical correction or up to the age of 5 years. In subsequent infections of a normal urinary tract, short course chemotherapy can be used.

UTI's are again a problem for males after the age of 50, when prostatic obstruction, urethral instrumentation and surgery influence the infection rate. Infection at an earlier age in a male is rare and requires careful evaluation for the presence of urinary tract pathology. Bacteriuria occurs commonly in debilitated elderly patients particularly those in long-stay institutions. The reasons include the high prevalence of prostatitis in males, poor bladder emptying and faecal incontinence. In elderly women, the loss of the oestrogen effect on the genito-urinary mucosa can be a factor.

Recurrent UTI's arise in many patients for various reasons which include gross anatomical abnormalities, development of resistance to the antibiotic used or a genetically predisposed
uroepithelium. These patients need thorough investigation and may need antibiotic prophylaxis to prevent infection.2,9

DURATION OF TREATMENT

- The traditional approach to treatment of lower UTI was 7 to 14 days of therapy but studies suggest that shorter 3 day courses are as effective.2,4,11,12
- In the majority of women with symptoms indicating uncomplicated UTI, cure rates with 3 day therapy with e.g. trimethoprim appear comparable to those achieved with longer courses.11
- Single dose regimens e.g. amoxycillin 3g, fosfomycin 3g have been evaluated for the treatment of uncomplicated UTI with varying cure rates (60-100%) reported. Further studies are required before they can be routinely recommended.2
- For bacteriuria of pregnancy, a 7 day course of e.g. nitrofurantoin should be followed by a repeat urine culture to confirm clearing of the organism.13,14
- Longer courses of up to 4-6 weeks are recommended for women who relapse early with the same organism, for patients with diabetes, polycystic kidney disease and for renal transplant recipients, all of whom are more likely to have complicated infections.12
- Short course therapy should not be used for men, for patients with pyelonephritis, symptoms lasting more than seven days, anatomical or functional abnormalities of the urinary tract, immunosuppression or indwelling catheters or in those who have a high probability of having resistant bacteria.8
- In children, treatment is usually given for seven days initially and may be followed by low dose prophylaxis until investigation of the urinary tract is completed.7

CHOICE OF DRUG

- A renally excreted antibiotic with a long half-life, effective in short courses with a low incidence of side-effects is ideally required in the treatment of UTI.
- Variation in antibiotic sensitivities exist between different areas and if a local antibiotic prescribing policy exists this should be adhered to.
- The choice depends on the likely susceptibility of the organism, ease of administration, efficacy, freedom from adverse effects and relative cost.

ANTI-FOLATES

This group includes trimethoprim and co-trimoxazole. Trimethoprim is the agent of choice in non-pregnant women with an uncomplicated UTI. Long term use does not increase resistance, it has a convenient twice daily dosage regimen, is inexpensive and does not interact with the oral contraceptive pill (OCP). It can be used in children, except during the first six months of life and is used for prophylaxis.7 Its main side-effects are skin reactions and gastrointestinal disturbances and it should not be used during pregnancy.5 Manufacturers recommend not to use during lactation although short-term use is not known to be harmful.

Co-trimoxazole is no longer recommended for the treatment of UTI because of sulphonamide associated toxicity.15,16
Nitrofurantoin is concentrated in the urine and does not promote resistance of organisms in faecal flora. It is thus ideally suited for prophylaxis. It can be used during pregnancy but should be avoided at term because of the risk of neonatal haemolysis.\(^5\) It can also be used during lactation, does not interfere with the OCP and its cost is acceptable to most patients.

Nausea can be a problem but may be overcome by taking with milk at bedtime or using the macrocrystalline form. Prolonged use may be complicated by rare pulmonary reactions and hepatitis. It should be avoided in patients with impaired renal function.\(^17,18\)

**Penicillins**

Due to resistance problems the penicillins should not be used unless the infection is known to be sensitive. They are safe to use during pregnancy and lactation and are relatively inexpensive. Diarrhoea, skin reactions, genital itching and vaginal problems are some of the adverse effects.\(^18\)

Co-amoxiclav has a broader spectrum of action than amoxicillin alone but is considerably more expensive and should be used as a second line agent. It has been used during pregnancy and is probably safe but experience is limited.

**Cephalosporins**

Cephalosporins are useful for UTI's which do not respond to other drugs. Characteristics of individual cephalosporins may vary. Cephalexin, cephradine, cefaclor and cefadroxil may be used with caution during pregnancy and lactation.\(^13\) They are also thought not to interact with the OCP.

Hypersensitivity is the main adverse effect. Resistant organisms are more commonly isolated in institutional settings or following multiple antibiotic exposures. Poor clinical and bacteriologic responses limit prescribing of these agents for UTI. They are more expensive than trimethoprim and should serve only as alternatives.

**Quinolones**

Nalidixic acid was the first of this group of antibiotics and is effective against most urinary pathogens. Relative disadvantages to its use include gastrointestinal intolerance, frequent dosing, avoidance in pregnancy and lactation and high cost. It should be avoided in neonates.\(^7\)

Newer agents include ciprofloxacin and ofloxacin. Their widespread use in general practice is not warranted and should only be used in resistant cases, in patients who cannot tolerate other agents, in nosocomial infections and in complicated UTI's.\(^10\) They should not be used in pregnancy, lactation or in children due to the risk of inducing arthropathy. They can interfere with the plasma concentration of theophyllines and increase prothrombin time during warfarin therapy.\(^18\) Enthusiasm for their widespread use in uncomplicated infections is dampened by the concerns of cost and emergence of resistant isolates.\(^2\)

**Others**

Aminoglycosides are frequently used in hospitals but do not have a role in the community as they require parenteral administration.

Tetracyclines are not recommended for UTI because of resistance problems. Doxycycline is sometimes used because less bacterial resistance develops, good urine concentrations are achieved and it can be given twice daily.\(^19\)

**Conclusion**

The therapeutic alternatives for the treatment of UTI's continue to increase. Understanding the key criteria for antibiotic selection, pathology of UTI and therapeutic profile of commonly prescribed agents will ensure rational, safe and cost-effective treatment for each patient.

Conventional inexpensive antibiotics can be used in most situations reserving the newer agents for certain indications such as hypersensitivity or intolerance to conventional agents and for infections caused by resistant micro-organisms.
COMPARATIVE DAILY COSTS FOR ANTIBIOTIC THERAPY IN THE TREATMENT OF
ACUTE LOWER URINARY TRACT INFECTIONS
Drug costs are based on data from GMS 1996.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit Cost (Dose: Cost for 28 Days)</th>
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<tbody>
<tr>
<td>Trimethoprim (Ipral/Monotrim)</td>
<td>£0.18 (200mg BD: £0.18)</td>
</tr>
<tr>
<td>Nitrofurantoin (Furadantin)</td>
<td>£0.42 (50mg QDS: £0.42)</td>
</tr>
<tr>
<td>Nitrofurantoin (Macrobid)</td>
<td>£0.60 (100mg BD: £0.60)</td>
</tr>
<tr>
<td>Nitrofurantoin (Macrodantin)</td>
<td>£0.49 (50mg QDS: £0.49)</td>
</tr>
<tr>
<td>Amoxycillin (Galenamox)</td>
<td>£0.30 (250mg TID: £0.30)</td>
</tr>
<tr>
<td>Co-amoxiclav (Augmentin)</td>
<td>£1.25 (1 tab TID: £1.25)</td>
</tr>
<tr>
<td>Cefaclor (Distacol)</td>
<td>£1.50 (250mg TDS: £1.50)</td>
</tr>
<tr>
<td>Cephalexin (Kemelex)</td>
<td>£1.50 (250mg QDS: £1.50)</td>
</tr>
<tr>
<td>Cephradine (Velosef)</td>
<td>£0.73 (250mg QDS: £0.73)</td>
</tr>
<tr>
<td>Nalidixic acid (Negram)</td>
<td>£1.76 (1g QDS: £1.76)</td>
</tr>
<tr>
<td>Ciprofloxacin (Ciproxin)</td>
<td>£1.61 (250mg BD: £1.61)</td>
</tr>
<tr>
<td>Ofloxacin (Tarivid)</td>
<td>£0.79 (200mg OD: £0.79)</td>
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COST OF PROPHYLAXIS OF UTI IN CHILDREN e.g. 2 year old (12.5kg)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit Cost (Dose: Cost for 28 Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim susp. (Monotrim 50mg/5ml)</td>
<td>£1.46/100ml (2.5ml nocte: £1.02)</td>
</tr>
<tr>
<td>Nitrofurantoin susp. (Furandantin 25mg/5ml)</td>
<td>£4.79/300ml (2.5ml nocte: £1.11)</td>
</tr>
<tr>
<td>Nalidixic Acid susp. (Negram 300mg/5ml)</td>
<td>£12.35/150ml (2.5ml nocte: £5.76)</td>
</tr>
<tr>
<td>Co-amoxiclav <em>(Augmentin paed. 100ml)</em></td>
<td>£3.95/100ml (5ml nocte: £15.80)</td>
</tr>
</tbody>
</table>

* Augmentin has shelf-life of one week when reconstituted
  All above suspensions are sugar-free

REFERENCES
15. WHO ADR Newsletter 1995; 4: 4
16. DTB, Dec 1995; 33 (12): 92-93
20. Paed Formulary; Guy's, Lewisham, 3rd Edition

Every effort has been made to ensure that this information is correct and it is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet for specific information on drug use.