Female lower urinary tract infection

Acute uncomplicated UTI
Extremely common
Risk factors
Sexual intercourse
Age of first UTI
Maternal UTI
History of recurrent UTIs
HLA-A3 and Lewis blood group antigen non-secretor status
Differential diagnosis
Acute urethritis
Chlamydia or gonorrhoea
Hx STD, discharge, odour and irritative LUTS
Acute vaginitis
Candida or Trichomanas vaginalis
Vaginal discharge, odour, irritation, dyspareunia, no LUTS
Acute cystitis
Enterobacteria
Irritative LUTS and dysuria
Haematuria in ~40%
Management
Depends on location and E. Coli sensitivity pattern

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefpodoxime</td>
<td>100 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Ciprofloxacin*</td>
<td>250 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>CiproXR*</td>
<td>500 mg od</td>
<td>3 days</td>
</tr>
<tr>
<td>Fosfomycin trometamol</td>
<td>3000 mg SD</td>
<td>1 day</td>
</tr>
<tr>
<td>Levofloxacin*</td>
<td>250 mg od</td>
<td>3 days</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50-100 mg tid,</td>
<td>5-7 days</td>
</tr>
<tr>
<td></td>
<td>100 mg SR bid</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin*</td>
<td>400 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Ofloxacin*</td>
<td>200 mg bid</td>
<td>3 days</td>
</tr>
<tr>
<td>Flumeccillinam</td>
<td>200 mg bid</td>
<td>7 days</td>
</tr>
<tr>
<td>Trimethoprim (TMP)*</td>
<td>200 mg bid</td>
<td>5-7 days</td>
</tr>
<tr>
<td>TMP-SMX*</td>
<td>160/800 mg bid</td>
<td>3 days</td>
</tr>
</tbody>
</table>

*Resistance rates of E. coli vary considerably within Europe. These substances are only recommended for empirical therapy when the resistance rate of E. coli is < (10%-20%).

CiproXR = ciprofloxacin sustained release; SMX = sulphonmethoxazole; od = once daily; bid = twice daily;
gid = four times daily; SD = single dose; SR = sustained release.

Considerations:
Single dose therapy less effective than short-course therapy
3-day course as effective as longer duration therapy for TMP-SMX and quinolones
TMP recommended instead of TMP-SMX (risk of hepatotoxicity, hypersensitivity, bone marrow suppression, methaemoglobinaemia and crystalluria)
TMP only recommended where resistance rates <20%
TMP-SMX a/w eradication rates of 85%
Quinolones a/w eradication rates of 95% - more expensive and therefore second-line – once daily preparations as effective vs. standard regimes
Beta-lactams and cephalosporins (except third generation oral cefpodoxime proxetil) not recommended
3 day course of nitrofurantoin not sufficient (5-7 days required)
Good activity of nitrofurantoin vs. E. Coli and S. Saprophyticus but no activity vs. P mirabilis and Klebsiella

**Recurrent UTI**
3 confirmed UTIs in 12 months or two in 6 months

**Risk factors**
- Frequency of intercourse
- Spermicide use
- Age of first UTI
- Maternal history of UTI
- HLA-A3 and Lewis blood group antigen non-secretor status

**Options:**
- Low dose prophylaxis
- Post-coital antibiotics
- Self-start therapy

*Caution in pre-menopausal women on the combined oral contraceptive pill.
Alteration of gut flora by Abx may affect absorption of ocp - additional contraception required. However if duration of Abx therapy > 3weeks, gut bacteria become resistant – no need for additional contraception.
Alternatively recommend other forms of contraception
  - Progestogen only pill (Cerazette 75ug) – not affected (see appendix)
  - Progestogen implant (Depo-provera, implanon)
  - IUCD
  - Barrier contraception

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>50 mg/day (98)</td>
</tr>
<tr>
<td>Nitrofurantoin macrocrystals</td>
<td>100 mg/day (101, 106)</td>
</tr>
<tr>
<td>Trimethoprim-sulphamethoxazole</td>
<td>40/200 mg/day (97) or three times weekly (110)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>100 mg/day (103)</td>
</tr>
<tr>
<td>Fosfomycin trometamol</td>
<td>3 g/10 day (109)</td>
</tr>
</tbody>
</table>

**Antibiotic prophylaxis**
Efficacy of antibiotic prophylaxis well-established. Cochrane review by Albert 2004 identified 19 studies involving 1120 women. In the studies of antibiotic vs. placebo, antibiotics were a/w 5-fold reduction in risk of UTI (RR 0.21; majority of studies used quinolones, typically cinoxacin – now discontinued)
Duration of prophylaxis not well-established. Some studies of TMP-SMX identified efficacy for as long as 5 yrs. Prophylaxis does not modify natural history of recurrent UTI: following cessation ~60% will experience re-infection within 6 months.

Post-coital prophylaxis
Appears as effective as continuous low-dose prophylaxis in young women (Melekos 1997), but more suitable and cost-effective.

Alternative therapies
(i) Cranberry juice/capsules
Believed to prevent adherence of E coli to uroepithelial cells (fructose prevents adherence of mannose-specific type 1 fimbriae; proanthrocyanidins prevent adhesion of type p pili)
Cochrane review 2004 (Jepson 2004)
Few good studies
Overall cranberry products significantly reduce risk of recurrent UTIs at 12 months (relative risk 0.65)
Risk reduction only in younger groups with recurrent symptomatic UTIs
Less evidence in elderly and with catheters
Efficacious volume not established (300ml used most often)
Tablets just as good and compliance may be higher (400mg/day)
Remarkably, no studies comparing cranberry capsules with standard antibiotic prophylaxis
(ii) Urinary acidification – minimal evidence
(iii) Vaginal application of lactobacilli (possibly in elderly – compliance low)
(iv) Immunological
Oral E coli fractions (Uro-vaxom)
One meta-analysis reports ~RRR 0.65 (Bauer 2002? quality)
Immunization with heat-killed bacteria
Very limited data – research interest only

Postmenopausal UTI
Risk factors
Vesical prolapse
Urinary incontinence
Elevated PVR
Reduced oestrogen - reduced lactobacilli – increased vaginal pH – UTI
Oestrogen replacement (Cochrane systematic review Perotta 2008)
No evidence that oral oestrogens reduce UTI
Reasonable evidence that intravaginal oestrogens reduce UTIs
Raz and Stamm NEJM 1993 – topical vaginal cream 0.5mg estriol daily for 2 weeks then twice weekly for 8 months
Reduced UTI (by approximately 75% cf. placebo)
Increased lactobacilli
Reduced vaginal pH
Reduced colonisation with enterobacteria
Minor vaginal itching and irritation

Efficacy for vaginal pessaries unclear. Raz reported less impressive results for pessaries than for cream (Raz 2003 – 0.5mg estriol twice weekly). BNF: Ortho-Gynest® (Janssen-Cilag)

- Intravaginal cream, estriol 0.01%. Net price 80 g with applicator = £2.43. Excipients include arachis (peanut) oil
- Condoms damages latex condoms and diaphragms
- Dose: Insert 1 applicatorful daily, preferably in evening; reduced to 1 applicatorful twice a week; attempts to reduce or discontinue should be made at 3–6 month intervals with re-examination

Vagifem® (Novo Nordisk)

- Vaginal tablets, f/c, m/r, estradiol 25 micrograms in disposable applicators. Net price 15-applicator pack = £7.92
- Condoms no evidence of damage to latex condoms and diaphragms
- Dose: Insert 1 tablet daily for 2 weeks then reduce to 1 tablet twice weekly; discontinue after 3 months to assess need for further treatment

Alternatively antibiotics as for pre-menopausal women. Efficacy of short-course medication less well established. Therefore treat with 5-7 days antibiotics

UTI in pregnancy

Common

Due to anatomical and physical changes of pregnancy

- Renal enlargement ~1cm
- Increased RBF and GFR (30-40%)
- Reduced peristalsis (progesterone) and relative obstruction 2’ gravid uterus
- Impaired bladder emptying
- Progesterone – smooth muscle relaxation
- Bladder displaced anteriorly and superiorly
- Increased expression of Dr adhesins (E coli)

Early localisation studies found ~50% from upper tract and ~50% lower tract

3 distinct, related entities: asymptomatic bacteruria, cystitis and pyelonephritis

Symptomatic UTIs a/w increased risk of low birth weight (<2500g), prematurity (<37 weeks) and perinatal mortality. Asymptomatic bacteruria not directly a/w these complications but increased risk of pyelonephritis.

Asymptomatic bacteruria

- Defined as two consecutive positive cultures > 10^5 cfu/ml of same species
- Incidence 4-7%
- A/w multiparity, low socioeconomic group, age and sexual activity
- Risk also increases with duration of pregnancy
Female lower urinary tract infection

Does not resolve spontaneously
Untreated a/w 20-40% chance of pyelonephritis (Kass 1960)
Treatment of asymptomatic bacteruria reduces incidence to less than 5%
Treatment typically based on sensitivities – 5-7 day course recommended
Follow-up cultures recommended to confirm eradication
If culture remains positive:
  Retreat and consider prophylaxis if rapid re-infection suspected

**Acute cystitis**
More common than pyelonephritis
Typical symptoms of dysuria frequency and urgency
Treatment with 7 days minimum recommended (see below)

**Acute pyelonephritis**
~2% of pregnancies
Three-quarters in third trimester
Historically in pre-antibiotic era a/w fetal and maternal complications
Admit for IV antibiotics – 2nd or 3rd generation cephalosporins, aminopenicillin + BLI, or aminoglycoside

Drug safety in pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Avoid In</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Macrolides</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Use with caution</td>
<td>Possible pre-term labour*</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>All</td>
<td>Skeletal abnormalities - T1 Teeth discolouration - T2/T3 Maternal liver dysfunction – All</td>
</tr>
<tr>
<td>Quinolones</td>
<td>All</td>
<td>Joint abnormalities – All</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>1st</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>2nd/3rd</td>
<td>Auditory/vestibular abnormalities</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>3rd</td>
<td>Grey baby (toxicity) at term</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>3rd</td>
<td>Neonatal haemolysis Methaemoglobinemia ?Kernicterus</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>3rd</td>
<td>Neonatal haemolysis</td>
</tr>
</tbody>
</table>

* Evidence re. metronidazole poor. Occasionally given in pregnancy to treat BV, which is itself associated with an increased risk of pre-term labour. An alternative would be co-amoxyclav or clindamicin, which have moderate anaerobic activity and are reportedly safe in pregnancy.
Table 5.1 The mode of action and side-effects of the antibiotics most commonly used in the treatment of UTIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Mode of action</th>
<th>Common side-effects and cautions</th>
<th>Relevance in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Bactericidal</td>
<td>Interference with bacterial cell wall synthesis</td>
<td>Hypersensitivity, diarrhoea</td>
<td>Safe</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Bactericidal</td>
<td>Interference with bacterial cell wall synthesis</td>
<td>Hypersensitivity, diarrhoea</td>
<td>Safe</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Bacteriostatic</td>
<td>Inhibition of ribosomal protein synthesis</td>
<td></td>
<td>Safe</td>
</tr>
<tr>
<td>(erythromycin, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>Bacteriostatic</td>
<td>Prevention of DNA replication by inhibition of DNA gyrase</td>
<td>Tendon damage (higher risk when given with steroids), diarrhoea, contraindicated in epileptics, interaction with warfarin</td>
<td>Unsafe</td>
</tr>
<tr>
<td>(ciprofloxacin, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Bacteriostatic</td>
<td>Inhibition of ribosomal protein synthesis</td>
<td>Hepatotoxicity, deposition in growing bones and teeth</td>
<td>Unsafe</td>
</tr>
<tr>
<td>Trinemethoprim</td>
<td>Bacteriostatic</td>
<td>Prevention of DNA replication by inhibition of dihydrofolate reductase</td>
<td></td>
<td>Unsafe in first trimester</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Bactericidal</td>
<td>Inhibition of ribosomal protein synthesis</td>
<td>Nephrotoxicity, ototoxicity, impairs neuromuscular transmission, caution in elderly and renal impairment</td>
<td>Unsafe in second and third trimesters</td>
</tr>
<tr>
<td>(gentamicin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Bactericidal</td>
<td>Damages bacterial DNA by inhibiting multiple enzyme systems</td>
<td>Acute and chronic lung toxicity, hepatotoxicity, allergic reactions, inadequate urine concentration at GFR &lt; 50</td>
<td>Unsafe in third trimester</td>
</tr>
</tbody>
</table>

Faculty of sexual and reproductive healthcare clinical guidance on POPs

13 Women using liver enzyme-inducing medications short term should be advised to use condoms in addition to progestogen-only pills and for at least 4 weeks after the liver enzyme-inducer is stopped. (Grade C)

14 Women using liver enzyme-inducing medications long term should be advised that the efficacy of progestogen-only pills is reduced and an alternative contraceptive method should be considered. (Grade C)

15 Women may be advised that the efficacy of progestogen-only pills is not reduced by use of non-liver enzyme-inducing antibiotics and additional contraceptive protection is not required. (Grade C)

Cerazette 75ug
BNF Guidelines on topical oestrogens and risk of malignancy

“A cream containing an oestrogen may be applied on a short-term basis to improve the vaginal epithelium in menopausal atrophic vaginitis. It is important to bear in mind that topical oestrogens should be used in the smallest effective amount to minimise systemic effects. Modified-release vaginal tablets and an impregnated vaginal ring are now also available.

The risk of endometrial hyperplasia and carcinoma is increased when systemic oestrogens are administered alone for prolonged periods (section 6.4.1.1). The endometrial safety of long-term or repeated use of topical vaginal oestrogens is uncertain; treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma”