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 2.3: Recommended antimicrobial regimens for the treatment of acute uncomplicated bacterial cystitis in adult premenopausal, non-pregnant women

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

**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 = sulphamethoxazole; od = once daily; bid = twice daily; qid = 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 2.6: Recommendations for antimicrobial prophylaxis of recurrent uncomplicated UTI in women (IA)

Agent[1]	Dose
Standard regimen:	
• Nitrofurantoin	50 mg/day (98)
• Nitrofurantoin macrocrystals	100 mg/day (101,106)
• Trimethoprim-sulphamethoxazole	40/200 mg/day (97) or three times weekly (110)
• Trimethoprim	100 mg/day (103)
• Fosfomycin trometamil	3 g/10 day (109)
'Breakthrough' infections:	
• Ciprofloxacin	125 mg/day (105)
• Norfloxacin	200-400 mg/day (101,111)
• Pefloxacin	800 mg/week (104)
During pregnancy:	
• Cephalexin	125 mg/day (99)
Cefaclor	250 mg/day (100)

[1] *Taken at bedtime.*

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)D

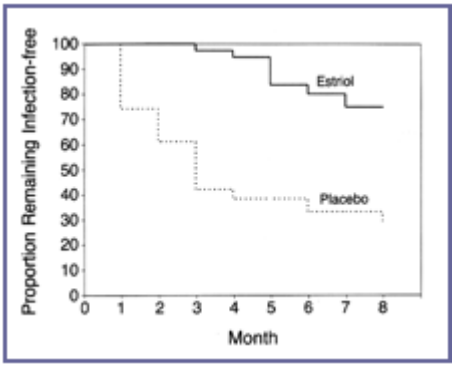
Duration of prophylaxis not well-established. Some studies of TMP-SMX identified efficacy for as long as 5 yrs
Prophylaxis does not modify natural history of recurrent UTI: following cessation ~ 60% will experience re-infection within 6 months

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; proanthrocyadinins 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 metaanalysis 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 oestogen - 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-couse medication less well established. Therefore treat with 5-7 days antbiotics

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.

<u>Asymptomatic bacteruria</u>

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

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 fequency 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

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

* 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.

Appendix

Table 9.1 The mode of action and side-effects of the antibiotics most commonly used in the treatment of UTIs

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

continued

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"