

## 1. Highlights

- ♦ **Acute uncomplicated cystitis in otherwise healthy ♀**
  - Short course - **3 day** therapy – suitable for cotrimoxazole (\$10), trimethoprim & fluoroquinolones (~\$20)
  - Nitrofurantoin (e.g. Macrobid) – a minimum of **7 days** treatment is recommended.
- ♦ **Fluoroquinolones** have excellent activity against most urinary pathogens; however concern that overuse is leading to increasing antimicrobial resistance. *Preserve them for those who really need them!*
- ♦ **Asymptomatic bacteriuria** in the institutionalized elderly is common. Antimicrobial treatment offers no benefit and increases the prevalence of resistant bacteria. *Don't culture asymptomatic residents.*

## 2. Oral Antimicrobials for Urinary Tract Infections

### Trimethoprim/Sulfamethoxazole or Cotrimoxazole (SMX/TMP) {Alternately consider monotherapy with Trimethoprim}

Coverage	♦ <i>E. coli, P. mirabilis, K. pneumonia, S. aureus</i>
Adverse effects	♦ diarrhea, rash, hematologic abnormalities (rare); (May use trimethoprim alone in sulpha allergic patients) (other less common effects: blood dyscrasias, diarrhea, pancreatitis, nephrotoxicity, urolithiasis, hepatotoxicity, hypersensitivity reactions, skin rash, toxic epidermal necrolysis & Stevens-Johnson syndrome. In patients with AIDS, cotrimoxazole produces an increased incidence of toxicity including a syndrome of fever, malaise, nausea and headache. Cotrimoxazole is also associated with disulfiram-like reactions.)
Drug interactions	♦ cyclosporine <sup>↑cyclosp levels &amp; ↑nephrotoxicity</sup> , digoxin <sup>↑dig levels</sup> , methotrexate <sup>↑MTX toxicity</sup> , metronidazole <sup>disulfiram reaction</sup> , phenytoin <sup>↑phenytoin toxicity</sup> , sulfonyleureas <sup>↑hypoglycemic effect</sup> , warfarin <sup>↑warf effect</sup>
Comments	♦ resistance is a problem especially in recurrent UTI; average reported resistance in SK is ~15%, however, higher in some institutional situations. Other antibiotics should be used when resistance ≥20%. ♦ maintain hydration

### Nitrofurantoin {Macrobid 100mg BID: well tolerated and convenient}

Coverage	♦ <i>E. coli, K. pneumonia, S. aureus, Enterococcus faecalis</i> ; (not <i>proteus, pseudomonas</i> )
Adverse effects	♦ rash, GI upset, increased LFTs; (other less common effects: pneumonitis and other pulmonary reactions, eosinophilia, hemolytic anemia, leukopenia, agranulocytosis, methemoglobinemia, peripheral neuropathy, pseudotumor cerebri, pseudomembranous colitis, nausea, vomiting, pancreatitis, parotitis, hepatitis, systemic lupus erythematosus and cutaneous and allergic reactions)
Drug Interactions	♦ Mg <sup>++</sup> antacids <sup>↓absorption</sup> , norfloxacin <sup>↓norfloxacin effect</sup> ; Food ↑'s absorption
Comments	♦ maintains excellent activity against <i>E. coli, Enterococci, &amp; Staph</i> ♦ avoid in renal dysfunction (CrCl <50ml/min); limited tissue penetration; <u>not</u> useful in complicated UTI

### Ciprofloxacin {Alternately, norfloxacin, gatifloxacin & levofloxacin; not moxifloxacin as lower concentration in urine}

Coverage	♦ <i>E. coli, P. mirabilis, K. pneumonia, P. aeruginosa, +/- S. aureus</i> (very broad coverage & effective agent)
Adverse effects	♦ headache, GI upset; (Other less common effects: CNS side effects, including seizures; increases in transaminases and in some cases severe and fatal hepatitis have developed. Additionally, hematuria and anaphylactic reactions have been described)
Drug Interactions	♦ antacids <sup>↓absorption</sup> ; may use a PPI / H2-antagonist; clozapine, glyburide <sup>↑hypoglycemia</sup> , iron <sup>↓cipro absorption</sup> , metoprolol <sup>↑metop level</sup> , phenytoin <sup>↑↓pheny levels</sup> , theophylline <sup>↑theoph toxicity</sup> , warfarin <sup>↑warf effect</sup> , zinc <sup>↓cipro absorption</sup> ; 1A2 substrates inhibited by ciprofloxacin & levofloxacin ∴ ↑ effect of olanzapine, haloperidol, imipramine, cyclobenzaprine, fluvoxamine, zolmitriptan...
Comments	♦ other fluoroquinolones also effective; <u>pseudomonal</u> coverage with ciprofloxacin & norfloxacin. ♦ lower doses suitable for uncomplicated UTI; higher doses for complicated UTI & pyelonephritis

### Amoxicillin/Clavulanic Acid (Amox/Clav)

Coverage	♦ <i>E. coli, P. mirabilis, K. pneumonia, S. aureus, Enterococcus faecalis</i>
Adverse effects	♦ rash, GI upset (diarrhea, more with q8h dosing <sup>~25%</sup> formulations than with q12h formulations <sup>~10%</sup> ) (Other less common effects: eosinophilia, leukopenia and thrombocytosis; superinfections resulting in candidal vaginitis and pseudomembranous colitis may occur. Caution in patients with a sensitivity to penicillin.)
Drug Interactions	♦ oral contraceptives <sup>↓contraceptive effect</sup> , methotrexate <sup>↓MTX clearance &amp; ↑toxicity</sup> ; Lab: false + 've Coomb's test
Comments	♦ good coverage for more resistant organisms including enterococcus.

### Fosfomycin - single dose

Comments	♦ usually less effective than SMX/TMP, esp for <i>S. saprophyticus</i> ; however <i>E. Coli</i> resistance uncommon Note: other beta-lactams (amoxicillin, 1 <sup>st</sup> gen cephalosporins) are alternatives although generally less effective clinically than SMX/TMP.
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## 3. Urban Outpatient Susceptibility Patterns (SK) – local susceptibility variation should be considered

- ♦ C&S results reflect patients with recurrent/more complicated infections as these patients getting are cultured most frequently
- ♦ **Frequency & susceptibility** of pathogens found vary depending on inpatient vs outpatient and complicating factors
- ♦ **Probable organisms:** Acute Cystitis ⇨ *E. coli, S. saprophyticus*; Complicated UTI ⇨ *E. coli, Enterococci, Klebsiella, Proteus, P. aeruginosa*  
Pyelonephritis ⇨ *E. coli, Klebsiella, Enterobacter, Proteus mirabilis*; Prostatitis ⇨ *E. coli, Gm -ve bacilli, Staph, enterococcus*
- ♦ *E. coli* (most common uropathogen): ≥83-87% S to SMX/TMP; ≥99% S to NTF; ≥94% S to Cipr; ≥82% S to Amox/Clav
- ♦ *Enterococcus*: Resistant to SMX/TMP ≥99% S to NTF; ≥74% S to Cipr; ≥98% S to Amp

**References:** 1. Anti-infective Review Panel. Anti-infective Guidelines for Community-acquired infections 2005, Toronto, ON (Canada). 1. Sanford Guide to Antimicrobial Therapy 2004. 3. Bugs and Drugs, [www.dobugsneeddrugs.org](http://www.dobugsneeddrugs.org). 4. Micromedex 2004 drug database. 5. Walker S, et al. Why are antibiotics prescribed for asymptomatic bacteriuria in institutionalized elderly people? CMAJ 2000;163:273-7. 6. Nicole L. Empirical treatment of acute cystitis in women. Int J Antimicrob Agents 2003;22:1-6. 7. Lummus W, Thompson I. Prostatitis. Emerg Med Clin N America 2001;19:691-707. 8. Warren J, et al. Guidelines for antimicrobial therapy of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Clin Infect Dis 1999;29:745-58. 9. Miller L. Treatment of Uncomplicated Urinary Tract Infections in an Era of Increasing antimicrobial Resistance. Mayo Clin Proc 2004;79:1048-1054. 10. Sask. resistance data from 2004 Antibiograms – Saskatoon (SHR) & Regina (RQHR). 11. McConnell JD, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. N Engl J Med. 2003 Dec 18;349(25):2387-2398. 12. Vogel T, et al. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women: a double-blind randomized controlled trial. CMAJ. 2004 Feb 17;170(4):469-73.

**URINARY TRACT INFECTIONS (UTI), ADULT – TREATMENT OPTIONS**

Prepared by: Loren Regier – [www.RxFiles.ca](http://www.RxFiles.ca)

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CLASS	Drug (Strength)		TRADE name	Comments (related to use for genitourinary infections)	Acute ♀ Cystitis >7days	Recurrent (<1mo)	Prophylact. see note re. dose	Pregnancy, Asymptomatic	Complicated Tx: x10-14 d	Pyeloneph. Out-patient	Pyeloneph. In-patient	Prostatitis <35yrs Acute; Tx x2-4wks	Typical Dose for Genitourinary Infections (↓ dose in ↓Renal Fx; consult additional references/ pharmacy if CrCl <10ml/min)	\$ 🇨🇦 (per 10 days)
	Shaded Rows = <b>IV Formulations</b>													
MISC. PO ABX	SMX/TMP (Cotrimoxazole) (100/20 <sup>5</sup> , 400/80 <sup>5</sup> mg, 800/160mg <sup>5</sup> DS tab; susp)		BACTRIM/SEPTRA (DS=double strength)	= sulfamethoxazole+trimethoprim; maintain hydration <i>E. coli</i> resistance ≤15% in SK; enterococci resistant	✓ x3d	✓ x10-14d	✓ *	✓ x3-7d	✓ C&S?	✓ C&S?	✓ C&S?	2 tabs (or 1 DS tab) PO BID ↓ dose if CrCl <30ml/min	10	
	Trimethoprim (100 <sup>5</sup> , 200 <sup>5</sup> mg tab)		PROLOPRIM	Alternative to SMX/TMP in sulpha allergy	✓ x7d	Except for acute cystitis, antimicrobial treatment guided by urine C&S; ↑ bacterial resistance in more complicated patient							100mg PO BID; 200mg OD	12
	Nitrofurantoin (50 <sup>5</sup> , 100 <sup>5</sup> mg tab)		NITROFURANTOIN	MACROBID well tolerated & convenient (BID) Effective 1 <sup>st</sup> line option in acute lower UTI. Note 7day therapy recommended for acute cystitis.	✓ x7d	✓ x10-14d	✓ *	✓ x3-7d	✓ C&S?	✓ C&S?	✓ C&S?	50mg PO QID cc Plain Avoid if CrCl <50ml/min Macro	14	
	Nitrofurantoin (50mg cap)		MACRODANTIN	Good activity vs <i>E. coli</i> ! (SE: rash, GI upset, ↑LFTs)	✓ x7d	✓ x10-14d	✓ *	✓ x3-7d	✓ C&S?	✓ C&S?	✓ C&S?	MACROBID 100mg PO BID cc	23	
	Nitrofurantoin (100mg cap)		MACROBID	Good activity vs <i>E. coli</i> ! (SE: rash, GI upset, ↑LFTs)	✓ x7d	✓ x10-14d	✓ *	✓ x3-7d	✓ C&S?	✓ C&S?	✓ C&S?	MACROBID 100mg PO BID cc	22	
PEN	Fosfomycin (3g oral powder sachet)		MONUROL	Single dose therapy; diarrhea <sup>9%</sup> ;	✓ x7d			✓ x3				3g PO x1; dissolve in ½ cup H <sub>2</sub> O	31	
	Amoxicillin (125, 250mg chew tab; 250, 500mg cap; susp)		AMOXIL	High rate >35% of <i>E. coli</i> resistance in SK! Option if C&S Ampicillin sensitive	✓ x7d			✓ x3-7d				500mg PO TID BID if CrCl <50ml/min	14	
	Amox/Clavulanate (susp) (250, 500, 875mg tab) –dose by amoxicillin component		CLAVULIN	Less <i>E. coli</i> resistance ~20% & broader coverage than amoxicillin; 875mg BID convenient & less diarrhea		✓ x7d			✓ x3	✓ x3		875mg PO BID 500mg if CrCl <50ml/min	37	
	Ampicillin (+AMG gent/tobra) IV		AMPICILLIN	Amp adds coverage for streptococcus & enterococcus					✓ x3		✓ x3	500mg-1g IV Q6H	70-90	
	Piperacillin/Tazobactam IV		TAZOCIN	Broad spectrum; covers pseudomonas; poor evidence					✓ x3			3g/0.375g IV Q6H ↓ dose if CrCl <50ml/min	700	
?	Imipenem IV		PRIMAXIN	Broad spectrum; covers pseudomonas; good evidence (Or: meropenem MERREM 500mg-1g IV q8h \$720-1,430)				✓ x3		✓ x3	500mg IV Q6-8H	999-790		
CEPH	Cephalexin (250, 500mg tab/cap; susp)		KEFLEX	Safe in pregnancy; option if C&S suggests sensitivity. <i>E. coli</i> resistance in SK ~10%	✓ x7d		✓ x3-7d					250-500mg PO QID	14-19	
	Ceftriaxone IV		ROCEPHIN	3 <sup>rd</sup> Gen IV Ceph's				✓ x3	✓ x3	✓ x3		1g IV Q24H	350	
	Cefotaxime IV		CLAFORAN	-no coverage of enterococcus				✓ x3	✓ x3	✓ x3		1g IV Q8-12H ↓ dose if CrCl <50ml/min	225-150	
	Ceftazidime IV		FORTAZ	Reserve ceftazidime → pseudomonal coverage				✓ x3	✓ x3	✓ x3		1g IV Q8H	200	
FQ	Norfloxacin (400mg tab)		NOROXIN	Fluoroquinolones (FQs) useful if allergy or intolerance to other agents. Reserve (preserve) for more severe, complicated or resistant infections. Concern regarding ↑ing resistance by both Gm-ve & Strep pneumo; CIPRO covers pseudomonas. Other FQs: moxifloxacin AVELOX 400mg po OD has lower renal concentrations therefore not indicated for UTI PO ≈ IV; consider early switch (IV → PO) e.g. 3-4days (Cipro 1g XL po od: 3 days=\$17, 10days=\$40)	✓ x3d	✓ x10-14d	✓ x3	AVOID	✓ x3	✓ x3	✓ x3	400mg PO BID ac	40	
	Ciprofloxacin (250, 500, 750mg tab; 500mg & 1g XL tab, susp)		CIPRO		Lower FQ dose option for cystitis; but higher doses for pyelonephritis & prostatitis	✓ x3d	✓ x10-14d	✓ x3	AVOID	✓ x3	✓ x3	✓ x3	250-500mg PO BID ↓ dose if CrCl <50ml/min	44-49
	Ciprofloxacin IV		CIPRO		Less pseudomonal coverage than Cipro! Urine C&S usually done for cipro.	✓ x3d	✓ x10-14d	✓ x3	AVOID	✓ x3	✓ x3	✓ x3	200-400mg IV Q12H	330-660
	Gatifloxacin (400mg tab) 200, 400mg inj		TEQUIN			✓ x3d	✓ x10-14d	✓ x3	AVOID	✓ x3	✓ x3	✓ x3	200-400mg PO OD Or IV ↓ dose if CrCl <50ml/min	36-67
	Levofloxacin (250, 500 & 750mg tab) 250, 500mg inj		LEVAQUIN/generic			✓ x3d	✓ x10-14d	✓ x3	AVOID	✓ x3	✓ x3	✓ x3	{250-500mg IV q24h \$175-350} 250-500mg PO OD	44-49
AMG	Gentamicin (+/- Ampicillin) IV		GARAMYCIN	Excellent Gm –ve coverage. Q24H dosing safe & effective; levels not necessary for <7day therapy				✓ x3	✓ x3	✓ x3	✓ x3	4-6mg/kg IV Q24H e.g. 300-350mg IV Q24H	45-50	
	Tobramycin IV		NEBCIN	Reserve tobramycin for pseudomonal coverage				✓ x3	✓ x3	✓ x3	✓ x3	adjust dose for ↓ renal fx	80-95	

**Suggested role in therapy:** ✓<sub>1</sub> = 1<sup>st</sup> line option; ✓<sub>2</sub> = 2<sup>nd</sup> line option; ✓<sub>3</sub> = 3<sup>rd</sup> line option. (References: 2005 Anti-infective Guidelines, Anti-infective Review Panel, Ontario; Sanford Guide-Antimicrobial Therapy 2004) ζ=scored tab  
 ↓ = dose for renal dysfunction; \$=10day cost (incl. markup & dispensing fee); ⚡ = Exception Drug Status Sask. ✕ = non-formulary in SK ▼ = covered by NIHB ⚡ = prior NIHB; avail. of IV formulations may vary. Consider STDs e.g. *C. trachomatis*: AMG= aminoglycoside C&S= culture & sensitivity CEPH= cephalosporins FQ= fluoroquinolones GI= gastrointestinal LFT= liver function tests PEN= penicillins SK= Saskatchewan ⇒ Doxy 100mg BID x7d or Azithro 1g x1

- ◆ **Acute Cystitis (uncomplicated)**: 3day tx option for SMX/TMP, TMP, FQs; 7day tx for nitrofurantoin, amoxicillin & cephalexin; longer course in: diabetes, symptomatic >7days (& older women?).
- ◆ **Recurrent Cystitis**: reassess, culture & treat 10-14days; Consider Prophylaxis: if 3+ episodes per year: e.g. SMX/TMP or TMP 100mg 1 tab qHS or post-coital; Nitrofurantoin 50mg qhs or post-coital; Cephalexin 250mg qhs or post-coital; Low-dose FQs (Cipro 250mg po or Norf 200mg) OD or every other day). Short-course patient-initiated treatment option for some; Vaginal estrogens option for post-menopausal ♀.
- ◆ **Antibiotics in Pregnancy**: ↑ = avoid nitrofurantoin at term (36+ weeks) ⇒ risk of hemolytic anemia; avoid SMX/TMP in last 6 weeks ⇒ displacement of bilirubin. Caution? TMP in 1<sup>st</sup> trimester; if used, give folic acid!
- ◆ **Complicated UTI**: includes men, obstruction, chronic catheter (symptomatic), structural abnormalities & spinal cord injury. Tend toward mixed bacteriology/more resistant organisms. C&S important!
- ◆ **Pyelonephritis**: Culture. Treat 10-14days (or ≥7 days for FQs). IV route if severe (convert from IV ⇒ PO after afebrile/improving x 1-2days); in diabetes & pregnancy, add ampicillin for Group B Strep.
- ◆ **Prostatitis**: if unable to void ⇒ hospitalization/catheterization. Chronic Prostatitis: may require longer duration of tx but often non-bacterial; if no response to ABX<sup>4-6wks</sup>, may refer; Other options: α-blockers!
- ◆ **Asymptomatic Bacteriuria - elderly, chronic cath., spinal cord injury**: no indications for screening & no benefit in treating (except pre-genitourinary procedures, pre-op prosthetic, immunosuppression)

Additional sources:

Thomas M. et al. Amoxicillin-Clavulanate vs Ciprofloxacin for the Treatment of Uncomplicated Cystitis in Women -a Randomized Trial. JAMA. 2005;293:949-955.