

FLUOROQUINOLONES

"Too Valuable to Overuse"

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The RxFiles
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Fluoroquinolone (FQ) Resistance - Is it really a concern? - Worldwide & Canadian Perspective

- FQ resistant strains of *S. pneumoniae*^{1,2,3,4}, *E. coli*, *Pseudomonas* and *gonococcus*⁵ have been identified and are emerging in Canada (see Figure 1 & Table 1).
- While resistance rates in many pathogens are still low, the slow emergence of resistant strains is concerning and could lead to the "demise of FQs as useful agents in the next 5-10 years"⁶ (IDSA-2003).

Reserving FQs for cases most likely to benefit from their use may preserve their long term effectiveness.

- Resistance is promoted with overuse, underdosing and lack of adjustment based on culture results.^{7,8}
- Useful Anti-infective References:

2005 Anti-infective Guidelines for Community-acquired Infections (CAN)⁹
2001 Do Bugs Need Drugs - www.dobugsneeddrugs.org (CAN-Alberta)¹⁰
2004 Sanford Guide to Antimicrobial Therapy (USA)¹¹
2004 Medical Letter Treatment Guidelines: Choice of Antibacterial Drugs¹²
2004 Johns Hopkins Antibiotic Guide - <http://www.hopkins-abxguide.org>¹³

Figure 1¹⁴: FQ resistant *S. pneumo* in Older Canadians

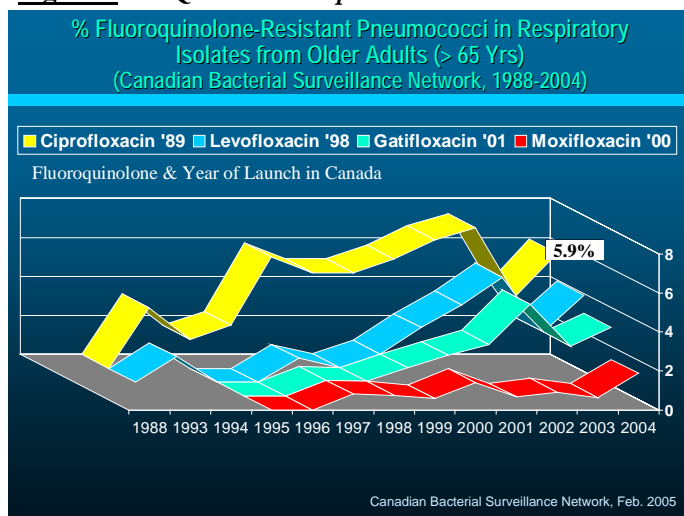


Table 1: How bad can FQ Resistance Be? Insight from Selected FQ Resistance Rates Worldwide (for ciprofloxacin unless otherwise noted)

Bacteria	Canada	World - Upper Range
<i>S. pneumoniae</i>	2.7% ¹⁵ ; 5.9% Elderly ¹⁴	14% levofloxacin - Hong Kong ¹⁶
<i>N. gonorrhoea</i>	4.4% Atlantic Canada ¹⁷	63% Korea, 92% China ¹⁸
<i>E. coli</i>	20% Nursing Home ¹⁹	22% Spain ²⁰
<i>Campylobacter</i>	<2% ²¹	84% Thailand ²²

Available 2005 Anti-infective Guidelines⁹ for Community-acquired Infections.
Anti-infective Review Panel : Now Available. Email: guidelines@mumshealth.com

FQs for respiratory tract infections (RTIs)?

- Respiratory FQs** (gati-, gemi-, levo- & moxi- floxacin) are quite effective for RTIs as they cover a broad spectrum of bacteria including atypicals such as *Chlamydia* and have good activity against *S. pneumoniae*.²³
- Several non-FQ alternatives are very effective in treating RTIs in lower risk individuals. A recent meta-analysis (in patients primarily <60yo; free of coexisting disease) found a modest benefit for FQs compared with oral macrolides, β -lactams, or doxycycline in community acquired pneumonia (CAP).²⁴ The authors indicated clinicians must decide whether 1 extra treatment success (i.e. symptom resolution only, not morbidity or mortality) for every 33 patients justifies initial treatment with a FQ and the potential increased FQ resistance.
- FQs are often appropriate for RTIs in patients with co-morbidity, more severe illness and those intolerant or resistant to alternative regimens.
- CAP**: FQs not indicated in previously healthy outpatients (suitable choice: macrolide or doxycycline).^{6,9,25,26,27}
- COPD, Acute Exacerbations**: Recommendations for low risk patients: amoxicillin, doxycycline, SMX/TMP, 2nd gen. cephalosporin or new macrolide e.g. azithromycin or clarithromycin. FQs or amoxicillin-clavulanate are useful for high risk patients (e.g. "Group 2 patients" - FEV1 < 50%, or have significant cardiac disease and/or experience 4 or more exacerbations per year.^{28(CND03), 29(NICE04)} FQ 5-7 day regimens are clinically equivalent but associated with greater eradication and longer disease free intervals compared to clarithromycin & other non-FQ comparators.^{30,31,32,33}
- Acute Bronchitis**: $\geq 90\%$ is viral without indication for antibiotics.^{9,11} If productive cough lasts 10+ days, a macrolide or doxycycline are considered 1st choice.⁹ In acute exacerbation of chronic bronchitis (**AECB**), FQs are reserved for more severe cases (as in COPD above).^{9,34(CND03)}
- Adult Sinusitis**^{35(2004),36,37,38}: FQs 3rd Line- if failed/severe disease (if symptomatic >7days \Rightarrow 1st Line: Amoxicillin; 2nd line: amox/clav, cefuroxime axetil, cefixime, doxycycline, clarithromycin, azithromycin & SMX/TMP).

When should ciprofloxacin be avoided?

- Ciprofloxacin has poor coverage of *S. pneumoniae*, and treatment failures have been reported. If a FQ is indicated for an RTI, a "respiratory FQ" with enhanced coverage of *S. pneumoniae* is preferred.
- Reserve ciprofloxacin for *Pseudomonas aeruginosa* e.g. bronchiectasis, cystic fibrosis, recent ICU stay, etc.

In cases of FQ treatment failure, it is most rational to choose an agent from a totally different antibiotic class.

Are FQs a good choice for treatment of acute (uncomplicated) cystitis in Saskatchewan?

- FQs should be reserved for recurrent, complicated, more severe or resistant cases.
- The most common urinary pathogen, *E. coli* generally responds to sulfamethoxazole/trimethoprim (SMX/TMP) or nitrofurantoin.³⁹ {In SK, cefazolin iv or cephalexin po may be an option ^{≥93% Susceptible-2003.}}
- E. coli* resistance rates to SMX/TMP (Sask.) are ~15%; however since many acute cystitis cases are not cultured, this **represents** *E. coli* from recurrent and/or more complicated cystitis.⁴⁰ Alternatives to SMX/TMP should be considered when resistance rates are ≥15-20%.^{41,42} Of interest SMX/TMP is clinically successful in >50% of women who appear to have resistant urinary pathogens.⁴⁰
- FQ or SMX/TMP regimens: A duration of 3 days** is recommended for healthy women with acute uncomplicated cystitis.^{43,44} Moxifloxacin has lower renal concentrations and is not indicated for UTI.
- Nitrofurantoin** has retained excellent activity against *E. coli* (≥98% susceptible ^{SK-2003}); however, **7 day regimens** are recommended for lower UTI.
- Related Note: in some regions, *N. gonorrhoea* resistance may also be an important consideration.
- See also *RxFiles* UTI Drug Comparison Chart⁴⁵

FQ Side Effect Concerns

- Glycemic reactions:** Rare hypo (within 3 days) & hyperglycemia (within 4-10 days esp. in very elderly), can occur in ~1% of patients on oral hypoglycemics (reported with most FQs)^{46,47,48}
- Minimal QT effects** (~1 per million prescriptions⁴⁹) for the current FQs, but reason grepafloxacin was removed. Caution for use if cardiac patients, concurrent drugs known to ↑ QT interval^{50,51} and if low potassium or magnesium. (Higher to Lower Antibiotic Risk: erythromycin; clarithromycin; gatifloxacin / levofloxacin / moxifloxacin)⁵²
- See also *RxFiles* Q&A-QT Prolongation...Feb05⁵³

Table 2: Antibiogram for Ciprofloxacin (SK)
(% isolates susceptible)

SK Region	<i>E. Coli</i>	<i>Klebsiella pneum.</i>	<i>Proteus mirabilis</i>	<i>P. aeruginosa</i>
S'toon Outpatient	99	96	99	72
S'toon Inpatient	98	98	100	78
RQHR Outpatient	94	97	91	78
RQHR Inpatient	95	97	87	81

Comment: FQs not necessarily drug of choice for bacteria listed.

Enterococcus: 56-74% susceptible to Cipro; use inadvisable except possibly in UTI
Saskatoon Health Region (S'toon) = **Jan 1999-Dec 2003** data (Note: 5 yrs of data)
Regina Qu'Appelle Health Region (RQHR) = **Apr 2003-Mar 2004** data

FQ dosages and comments are available in the *RxFiles* Anti-infective⁵⁴, Pneumonia (CAP)⁵⁵, & UTI⁴⁵ charts at www.RxFiles.ca

Table 3: FQ Pharmacological Overview^{23,56,57,58,59}

	Cipr CIPRO	Gati ⁶⁷ TEQUIN	Gemi FACTIVE	Levo ⁶⁸ LEVAQUIN	Moxi ⁶⁹ AVELOX	Norf NOROXIN	Oflo FLOXIN
Mechanism of Action	bactericidal; inhibition of DNA synthesis by interfering with DNA gyrase (topoisomerase II) and type IV topoisomerase						
Pharmacokinetics / Pharmacodynamics	Absorption: excellent bioavailability (>90-99%) (less with gemi) Distribution: widely distributed (except Moxi - low renal concentrations ⁶⁰) Elimination: renal & non-renal routes; (Moxi OK in renal dysfunction) - ↓ renal function: ↓ dose for Cipr, Gati, Gemi, Levo, Norf, Oflo concentration-dependent killing; post-antibiotic effect of 1-2 hours						
Side Effects {generally well tolerated}	<ul style="list-style-type: none"> Gastrointestinal 2-10%: nausea, anorexia, dyspepsia & other CNS toxicity 1-2%: headache, dizziness, drowsiness; less common: insomnia, agitation; rare-seizures esp. in elderly⁶¹ {least with Levo} Hepatic rare: elevation of enzymes (esp. with trovafloxacin) Dermatologic 0.5-3%: phototoxicity {least with Moxi/Gati}, rash, itch {Severe rash of some concern with Gemi. given limited clinical experience} Musculoskeletal ≤1%: arthropathy, tendinitis, achilles rupture Other hypo- or hyper-glycemia (usually in diabetics; especially with Gati) 						
Contraindications	<ul style="list-style-type: none"> Children <18 years of age^{62,63} (Except ciprofloxacin for postexposure anthrax & 2nd line in complicated <i>E. coli</i>/UTI/pyelonephritis in ≥1yr)^{American} Pregnancy category C⁶⁴ 						
Drug Interactions (select) ⁶⁵	<ul style="list-style-type: none"> Chelation with cations: Al⁺⁺(sucralfate), Mg⁺⁺, Ca⁺⁺, Fe⁺⁺, Zn⁺⁺ {avoid interaction by administering FQ >2 hrs before food/supplement} Drugs prolonging QT interval, especially in high-risk pts eg. Class 1A (quinidine, procainamide) & Class III (amiodarone, sotalol) antiarrhythmics; antidepressants, antipsychotics, azole antifungals, cisapride, clarithromycin & erythromycin. Ciprofloxacin: ↑ phenytoin, theophylline; All FQs: ↑ warfarin effect Gatifloxacin: ↑ digoxin levels/toxicity NSAIDs: may ↑ risk of CNS stimulation & seizures Rifampin: ↓ effectiveness of ciprofloxacin vs <i>S. aureus</i> 						
Relative Antimicrobial Activity Overview & Cost of FQs ⁶⁶							
Enterobacteriaceae	+++	+++	+++	+++	+++	+++	+++
Atypicals	+	+++	+++	+++	+++	+	+++
<i>S. pneumoniae</i> & PRSP	+	+++	+++	++	+++	-	+
<i>S. aureus</i>	+	++	++	+	++	-	+
<i>P. aeruginosa</i>	++	+/-	+/-	+/-	+/-	+ if UTI	-
Anaerobes	-	+	+	-	+	-	-
Indications * CANADA	ABCDEF ^{GH} IJK	ABCD ^G	B	ABCDEF	ABC	DG	BCEFGLM
Year launched CANADA	1989	2001	2005	1998	2000	1986	1995
Forms	Tab: 250, 500, 750mg Eye solns: for Cipr, Gati, Moxi & Oflo; Otic: Cipr.) 500mg XL [®] , 1g XL Susp: 500mg/5ml IV: 200, 400mg	Tab: 400mg 200mg ^x [®]	Tab: 320mg	Tab: 250, 500mg (750mg ^x [®]) IV: 500mg	Tab: 400mg IV: 400mg	Tab: 400mg	Tab: 200, 300 & 400mg
Dosing frequency	bid; XL form od	od	od	od	od	bid	bid ac
COST (10days therapy, unless noted)	\$44 250mg q12h \$49 500mg q12h \$40 1g XL [®] ▼	\$ 67	NA	\$49 500mg od \$63 750mg od [®]	\$ 69	\$40	\$ 67

Cipr=ciprofloxacin **CIPRO**, Gati=gatifloxacin **TEQUIN**, Gemi=gemifloxacin **FACTIVE**, Levo=levofloxacin **LEVAQUIN**, Moxi=moxifloxacin **AVELOX**, Norf=norfloxacin **NOROXIN**, Oflo=ofloxacin **FLOXIN**, NA=not available PRSP= penicillin resistant streptococcal pneumonia, **X** Non formulary Sask., **⊕** EDS in Sask., **⊗** =prior approval for NIHB **⊗**=not covered by NIHB **▼** covered by NIHB
Enterobacteriaceae include: *E. coli*, *Klebsiella*, *Enterobacter*, *Providentia*, *Serratia*, etc., **ac**=before meal
Atypicals include: *Chlamydia*, *Legionella*, *Mycoplasma*.
* **Indications, official** ^{CDN}: **A**=acute sinusitis; **B**=acute exacerbation of chronic bronchitis; **C**=CAP; **D**=complicated UTI/pyelonephritis; **E**=skin infections; **F**=chronic prostatitis; **G**=gonorrhoea; **H**=bone & joint; **I**=diarrhea; **J**=typhoid; **K**=neutropenia; **L**=pelvic inflammatory disease; **M**=Chlamydia

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References: RxFiles – www.RxFiles.ca – **FLUOROQUINOLONES**

- ¹ Ho PL, Tse WS, Tsang KW, et al. Risk factors for acquisition of levofloxacin-resistant Streptococcus pneumoniae: a case-control study. *Clin Infect Dis*. 2001 Mar 1;32(5):701-7. Epub 2001 Feb 28.
- ² Davidson R, Cavalcanti R, Brunton JL, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N Engl J Med*. 2002 Mar 7;346(10):747-50.
- ³ Chen DK, McGeer A, de Azavedo JC, Low DE. Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. *Canadian Bacterial Surveillance Network*. *N Engl J Med*. 1999 Jul 22;341(4):233-9.
- ⁴ Powis J, McGeer A, Green K, Vanderkooi O, Weiss K, Zhanel G, Mazzulli T, Kuhn M, Church D, Davidson R, Forward K, Hoban D, Simor A, Low DE; Canadian Bacterial Surveillance Network. In vitro antimicrobial susceptibilities of Streptococcus pneumoniae clinical isolates obtained in Canada in 2002. *Antimicrob Agents Chemother*. 2004 Sep;48(9):3305-11.
- ⁵ Fenton KA, Ison C, Johnson AP, et al.; GRASP collaboration. Ciprofloxacin resistance in Neisseria gonorrhoeae in England and Wales in 2002. *Lancet*. 2003 May 31;361(9372):1867-9. [also see Canadian Gonorrhoea Treatment Guidelines 2004 Update - http://www.phac-aspc.gc.ca/std-mts/is-gonorrhoea-2004_e.html]
- ⁶ Mandell LA, Bartlett JG, Dowell SF, et al.; **Infectious Diseases Society of America**. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis*. 2003 Dec 1;37(11):1405-33. Epub 2003 Nov 03 <http://www.journals.uchicago.edu/CID/journal/issues/v37n11/32441/32441.web.pdf>
- ⁷ Conly J. Antimicrobial resistance in Canada. *CMAJ*. 2002 Oct 15;167(8):885-91.
- ⁸ **Acute Otitis Media Guideline 2004** from the American Academy of Pediatrics & Family Physicians <http://aappolicy.aappublications.org/cgi/reprint/pediatrics;113/5/1451.pdf>
- ⁹ **2005 Anti-infective Guidelines for Community-acquired Infections**. Anti-infective Review Panel. (Canada) {Phone 416-597-6867; Fax 416-597-8574; Email guidelines@mumshealth.com }
- ¹⁰ **Bugs & Drugs Antimicrobial Pocket Reference 2001** (Canada-Alberta) <http://www.dobugsneeddrugs.org/healthcare/index.html>
- ¹¹ **Sanford Guide to Antimicrobial Therapy, 2004**. <http://www.sanfordguide.com>
- ¹² Treatment Guidelines: Choice of **Antibacterial Drugs**. *The Medical Letter*: March, 2004; (2) pp. 13-26.
- ¹³ **Johns Hopkins Antibiotic Guide 2004** – Online / PDA; <http://www.hopkins-abxguide.org>
- ¹⁴ Canadian Bacterial Surveillance Network. http://microbiology.mtsinai.on.ca/data/sp/sp_2003.shtml#figure7 {1998-2004 data}
- ¹⁵ Canadian Bacterial Surveillance Network. Canadian. Accessed Dec 22, 2004 at http://microbiology.mtsinai.on.ca/data/sp/sp_can.shtml {2002 data}
- ¹⁶ Felmingham D, Reinert RR, Hirakata Y, Rodloff A. Increasing prevalence of antimicrobial resistance among isolates of Streptococcus pneumoniae from the PROTEKT surveillance study, and comparative in vitro activity of the ketolide, telithromycin. *J Antimicrob Chemother*. 2002 Sep;50 Suppl S1:25-37. http://jac.oupjournals.org/cgi/reprint/50/suppl_2/25 {2000 data}
- ¹⁷ Sarwal S, Wong T, Sevigny C, Ng LK. Increasing incidence of ciprofloxacin-resistant Neisseria gonorrhoeae infection in Canada. *CMAJ*. 2003 Apr 1;168(7):872-3. Accessed online Dec 22, 2004 at <http://www.cmaj.ca/cgi/reprint/168/7/872.pdf> {2001 data}
- ¹⁸ Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention, Division of Sexually Transmitted Diseases Prevention (WHO SPR GASP 2002). Updated April 2004; Accessed Dec 22, 2004. <http://www.cdc.gov/std/gisp/IncreasedPrevAreas.htm> {2002 data}
- ¹⁹ Canadian Bacterial Surveillance Network, Issue 1, May 2002. Accessed online Dec 22, 2004 at <http://microbiology.mtsinai.on.ca/research/cbsnews/may02-news.pdf> {2002 data}
- ²⁰ Miller LG, Tang AW. Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. *Mayo Clin Proc*. 2004 Aug;79(8):1048-53; quiz 1053-4. Review. PMID: 15301333 Accessed online Dec 22, 2004 at <http://www.mayo.edu/proceedings/2004/aug/7908crc.pdf> (1999 data)
- ²¹ Ontario Government Report - Antimicrobial Susceptibility of Campylobacter jejuni and Campylobacter coli Isolated From Human and Poultry Samples in Ontario 1999. Accessed Online - <http://www.gov.on.ca/OMAFRA/english/livestock/animalcare/amr/facts/valdivieso.htm> (1999 data)
- ²² Hoge CW, Gambel JM, Srijan A, et al. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. *Clin Infect Dis*. 1998 Feb;26(2):341-5. {1995 data}
- ²³ Zhanel GG, Ennis K, Vercaigne L, Walky A, Gin AS, Embil J, Smith H, Hoban DJ. A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs*. 2002;62(1):13-59.
- ²⁴ Salkind AR, Cuddy PG, Foxworth JW. Fluoroquinolone treatment of community-acquired pneumonia: a meta-analysis. *Ann Pharmacother*. 2002 Dec;36(12):1938-43.
- ²⁵ Mandell LA et al. **Canadian** guidelines for initial management of community acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis* 2000; 31: 383-421.
- ²⁶ Treatment Guidelines: **Drugs for Pneumonia**. *The Medical Letter*: Sept., 2003; (13) pp. 83-88.
- ²⁷ Jones RN, Sader HS, Fritsche TR. Doxycycline use for community-acquired pneumonia: contemporary in vitro spectrum of activity against Streptococcus pneumoniae (1999-2002). *Diagn Microbiol Infect Dis*. 2004 Jun;49(2):147-9.
- ²⁸ **Canadian Thoracic Society COPD Guidelines: 2003**. *Can Respir J*. 2003 May-Jun; Suppl A. http://www.pulsus.com/Respir/10_SA/contents.htm
- ²⁹ National Institute for Clinical Excellence (NICE) -**COPD Guidelines Feb 2004** http://www.nice.org.uk/pdf/CG012_niceguideline.pdf
- ³⁰ Wilson R, Kubin R, Ballin I, et al. Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *J Antimicrob Chemother*. 1999 Oct;44(4):501-13.
- ³¹ Wilson R, Langan C, Ball P, et al.; Gemifloxacin 207 Clinical Study Group. Oral gemifloxacin once daily for 5 days compared with sequential therapy with i.v. ceftriaxone/oral cefuroxime (maximum of 10 days) in the treatment of hospitalized patients with acute exacerbations of chronic bronchitis. *Respir Med*. 2003 Mar;97(3):242-9.
- ³² Wilson R, Schentag JJ, Ball P, Mandell L; 068 Study Group (**GLOBE**). A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther*. 2002 Apr;24(4):639-52.
- ³³ Wilson R, et al.; **MOSAIC** Study Group. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest*. 2004 Mar;125(3):953-64.
- ³⁴ Balter MS, La Forge J, Low DE, Mandell L, Grossman RF; Canadian Thoracic Society; Canadian Infectious Disease Society. Canadian guidelines for the management of acute exacerbations of chronic bronchitis (**AECB**). *Can Respir J*. 2003 Jul-Aug;10 Suppl B:3B-32B. Review. Accessed 05Jan05 at http://www.pulsus.com/Respir/10_SB/balter_guidelines.pdf.
- ³⁵ Anon JB, Jacobs MR, Poole MD, Ambrose PG, Benninger MS, Hadley JA, Craig WA; Sinus And Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial **rhinosinusitis**. *Otolaryngol Head Neck Surg*. 2004 Jan;130(1 Suppl):1-45.
- ³⁶ American Academy of Pediatrics. Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics*. 2001 Sep;108(3):798-808. <http://pediatrics.aappublications.org/cgi/reprint/108/3/798.pdf>
- ³⁷ Snow V, Mottur-Pilson C, Hickner JM; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine; Centers for Disease Control; Infectious Diseases Society of America. Principles of appropriate antibiotic use for acute sinusitis in adults. *Ann Intern Med*. 2001 Mar 20;134(6):495-7. <http://www.annals.org/cgi/reprint/134/6/495.pdf>
- ³⁸ Osguthorpe JD. Adult rhinosinusitis: diagnosis and management. *Am Fam Physician*. 2001 Jan 1;63(1):69-76. <http://www.aafp.org/afp/20010101/69.pdf>
- ³⁹ Nicolle LE. Empirical treatment of acute cystitis in women. *Int J Antimicrob Agents*. 2003 Jul;22(1):1-6
- ⁴⁰ Miller LG, Tang AW. Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. *Mayo Clin Proc*. 2004 Aug;79(8):1048-53.
- ⁴¹ Fihn SD. Clinical practice. Acute uncomplicated urinary tract infection in women. *N Engl J Med*. 2003 Jul 17;349(3):259-66.
- ⁴² WJ McIsaac, T Mazzulli, R et al.; Uropathogen antibiotic resistance in adult women presenting to family physicians with acute uncomplicated cystitis. *Can J Inf Dis Med Microbiol*. 2004;15: 266-270.
- ⁴³ Nicolle LE. Empirical treatment of acute cystitis in women. *Int J Antimicrob Agents*. 2003 Jul;22(1):1-6
- ⁴⁴ Vogel T, Verreault R, Gourdeau M, Morin M, Grenier-Gosselin L, Rochette L. Optimal duration of antibiotic therapy for uncomplicated urinary tract infection in older women (age > 65; mean age 78): a double-blind randomized controlled trial. *CMAJ*. 2004 Feb 17;170(4):469-73. <http://www.cmaj.ca/cgi/content/full/170/4/469>
- ⁴⁵ RxFiles UTI Treatment Options Chart <http://www.rxfiles.ca/acrobat/CHT-UTI-Tx.pdf>
- ⁴⁶ Canadian Adverse Reaction Newsletter July 2003 http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adrv13n3_e.pdf
- ⁴⁷ Hypoglycemia and Hyperglycemia with Fluoroquinolones. *The Medical Letter*: August 4, 2003; pp. 64-65.
- ⁴⁸ Taylor S, Simor A, Cornish W et al. Analysis of Spontaneous Reports of Hypoglycemia and Hyperglycemia Associated with Marketed Systemic Fluoroquinolones Made to the Canadian Adverse Drug Reaction Monitoring Program. *CJHP* 2004 Feb;57(10):12-17.
- ⁴⁹ Rubinstein E, Camm J. Cardiotoxicity of fluoroquinolones. *J Antimicrob Chemother*. 2002 Apr;49(4):593-6.
- ⁵⁰ Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004 Mar 4;350(10):1013-22.
- ⁵¹ Drugs that Prolong the QT Interval +/- Induce Torsades de Pointes List <http://www.qtdrugs.org>
- ⁵² Iannini PB. Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. *Expert Opin Drug Saf*. 2002 Jul;1(2):121-8.
- ⁵³ RxFiles Q&A: QT Prolongation and Torsades De Pointes: Drugs and Sudden Death. Feb 2005. Accessed at www.rxfiles.ca.
- ⁵⁴ RxFiles Anti-infective Oral Comparison Chart <http://www.rxfiles.ca/acrobat/CHT-ABX-2P.pdf>
- ⁵⁵ RxFiles Community Acquired Pneumonia Selection Chart <http://www.rxfiles.ca/acrobat/cht-cap.pdf>
- ⁵⁶ Micromedex 2004
- ⁵⁷ Oliphant CM, Green GM. Quinolones: a comprehensive review. *Am Fam Physician*. 2002 Feb 1;65(3):455-64.
- ⁵⁸ Fish DN. Fluoroquinolone adverse effects and drug interactions. *Pharmacotherapy*. 2001 Oct;21(10 Pt 2):253S-272S.
- ⁵⁹ Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. *Emerg Infect Dis*. 2003 Jan;9(1):1-9. <http://www.cdc.gov/ncidod/EID/vol9no1/pdfs/02-0277.pdf>
- ⁶⁰ Paladino JA. Is more than one quinolone needed in clinical practice? *Ann Pharmacother*. 2001 Sep;35(9):1085-95.
- ⁶¹ Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. *Drugs Aging*. 2003;20(4):289-302.
- ⁶² Grady R. Safety profile of quinolone antibiotics in the pediatric population. *Pediatr Infect Dis J*. 2003 Dec;22(12):1128-32.
- ⁶³ Chalumeau M, et al.; Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. *Pediatrics*. 2003 Jun;111(6 Pt 1):e714-9.
- ⁶⁴ Briggs GG, Freeman RK, Sumner JY. **Drugs in Pregnancy and Lactation 6th Edition**. Williams & Wilkins, Baltimore, 2002.
- ⁶⁵ Hansten, PD and Horn JR. **Drug Interactions Analysis and Management**. Applied Therapeutics Incorporated. Vancouver, WA. 2004.
- ⁶⁶ Saravolatz LD, Leggett J. Gatifloxacin, gemifloxacin, and moxifloxacin: the role of 3 newer fluoroquinolones. *Clin Infect Dis*. 2003 Nov 1;37(9):1210-5. Epub 2003 Oct 02.
- ⁶⁷ Perry CM, Ormrod D, Hurst M, Onrust SV. Gatifloxacin: a review of its use in the management of bacterial infections. *Drugs*. 2002;62(1):169-207.
- ⁶⁸ Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs*. 2003;63(24):2769-802.
- ⁶⁹ Keating GM, Scott LJ. Moxifloxacin: a review of its use in the management of bacterial infections. *Drugs*. 2004;64(20):2347-77.