Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: January 2013 **Date of Last Review:** November 2009
PDL Classes: Fluoroquinolones, Oral **Source Document:** Provider Synergies

Current Status of PDL Class:

- Preferred Agents: Ciprofloxacin suspension and tablets, levofloxacin solution and tablets, norfloxacin
- Non Preferred Agents: Ciprofloxacin ER (CIPRO XR®, PROQUIN XR®), moxifloxacin (AVELOX®), ofloxacin, gemfloxacin (FACTIVE®)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Recommend inclusion of at least one medication with pseudomonas coverage and at least one "respiratory" quinolone (gemifloxacin, levofloxacin, moxifloxacin).

Methods:

A Medline OVID search was conducted with the following search terms: fluoroquinolones, ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, prostatitis, bronchitis, COPD, COPD exacerbation, sexually transmitted disease, chlamydia, gonorrhea, osteitis, osteomyelitis, otitis externa, typhoid fever, pyelonephritis, urinary tract infection, enterocolitis, tuberculosis, mycobacterium infection, chancroid, cholera, cholangitis, Crohn's disease, gastroenteritis, endocarditis, meningococcal infection, peritonitis, Plague, Pseudomonas, pneumonia, intestinal infectious disease, epididymitis, urethritis, respiratory tract infection, community acquired pneumonia, Mycobacterium Avium infection, Helicobacter Pylori, gastrointestinal tract infection, otitis media, sinusitis, Pelvic Inflammatory Disease, diarrhea, peritonitis, Anthrax, and Cystic Fibrosis. The search was limited to English language articles of controlled trials conducted on humans published from 2009 to October week 4 2012.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

New Trials:

A total of 201 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or other antibiotic class), or outcome (non-clinical). After a review of titles and abstracts for inclusion, five relevant head-to-head trials were identified. See Appendix 1 for complete trial abstracts.

Two trials examined the use of moxifloxacin for uncomplicated Pelvic Inflammatory Disease (PID). Heystek and Ross[1] randomized 434 women to moxifloxacin or combination doxycycline, metronidazole and ciprofloxacin for 14 days. The results of this double-blind, multi-center trial showed moxifloxacin was non-inferior to the combination regimen with the overall clinical success rates at 2–14 days post-therapy were 96.6% (moxifloxacin) and 98.0% (comparator) (95%CI: −4.5, 1.6). Clinical success was not defined. Only the abstract was available for review and the quality of the trial was therefore not evaluated.

Judlin et al[2] also examined moxifloxacin for uncomplicated PID. This fair quality randomized, double-blind, multi-center trial evaluated moxifloxacin versus levofloxacin plus metronidazole in 460 women for 14 days. The primary outcome was

clinical response 7–14 days after the last dose. Clinical response was defined as a reduction in the tenderness score, apyrexia and WBC <10 500/mm^3. Moxifloxacin was found to be non-inferior to levofloxacin plus metronidazole: 78.4% (moxifloxacin) and 81.6% (comparator) (95% CI: −10.7, 4.9). Both treatments were considered well-tolerated with nausea as the most common side effect for both groups.

Marom et al[4] conducted an open label phase II trial comparing two ciprofloxacin formulations for acute otitis media (AOE) in adults. The fair quality study randomized 64 patients to either foam-based or solution-based ciprofloxacin; all patients received medication twice daily for seven days. The primary efficacy outcome was infection cure by day 8 to 14. All patients included in the analysis achieved this outcome (defined as improvement or resolution of symptoms). No significant differences were found between treatments.

New drugs, formulations, or indications:
None

New FDA safety alerts:
No new safety alerts were released since 2009; however the FDA required several safety label changes for fluoroquinolones. In 2011, the FDA added the warning for potential increased intracranial pressure for ciprofloxacin[5] and gemifloxacin[6]. In 2012, moxifloxacin[7] labeling was altered to include a warning for increased risk of developing peripheral neuropathy. Lastly, the FDA added a warning to all systemic fluoroquinolones[8] concerning risk for exacerbation of Myasthenia Gravis in patients with a history of the condition.

In 2012, a case-control study published in the Journal of the American Medical Association found that patients who take fluoroquinolones are at an increased risk of retinal detachment, although the absolute risk for developing the condition remains small.[9] Absolute increase in risk of retinal detachment was 4 per 10,000 person-years.

New Systematic Reviews: (Appendix 2)

A new systematic review by Ziganshina et al[10] evaluated the use of fluoroquinolones for tuberculosis (TB) for the Cochrane Collaboration. This systematic review included 11 randomized and quasi-randomized trials with 1,514 participants. Study quality varied greatly; allocation concealment was described in only one trial, and blinding was either unclear or not done in seven of the trials. The primary outcome was cure of disease: defined as a negative sputum culture at both week eight and the end of treatment. Three interventions were studied. The first intervention looked at the efficacy of a fluoroquinolone (ciprofloxacin, moxifloxacin or ofloxacin) substituted into the TB regimen for rifampin, ethambutol or pyrazinamide plus ethambutol. No difference was found in either the rate of treatment cure or failure; however, use of ciprofloxacin or ofloxacin was associated with a higher incidence of relapse (RR 7.17, 95% CI: 1.33, 38.58). The second intervention compared standard TB treatment with and without the addition of levofloxacin. The third intervention compared the efficacy of substituting levofloxacin or ofloxacin for rifampin in TB treatment. No difference was found in treatment cure or failure between the two fluoroquinolones. The authors concluded although fluoroquinolones have anti-tubercular activity, they should not be substituted for standard TB treatment.

In another Cochrane Collaboration systematic review, Rafalsky et al[11] examined the use of fluoroquinolones for uncomplicated cystitis in women. The objective of the analysis was to compare efficacy, safety and tolerability amongst fluoroquinolones. This systematic review included 11 randomized and quasi-randomized trials with 7,535 women aged 16 and older. Study quality was mostly good; allocation concealment was described in all but one trial, seven trials described the randomization process and double-blinding was explicitly stated for ten of the trials. No trial used the same comparators and many fluoroquinolones included are not available in the US. The authors felt that none of the quinolones showed any advantage for efficacy in treating cystitis. Differences were seen for safety and tolerability. One study showed ofloxacin was more likely to cause adverse events (RR 0.8, 95% CI: 0.65, 0.99) than ciprofloxacin. In another study, adverse events were higher for ofloxacin (RR 0.45, 95% CI 0.22, 0.93) than levofloxacin. There was insufficient evidence to recommend one fluoroquinolone over another.

Guidelines:
Updated guidelines for sexually transmitted infections[12] from the Center of Disease Control (CDC) were reviewed for such relevant topics as chlamydia, pelvic inflammatory disease, cystitis, urethritis, and epididymitis. The World Health Organization updated drug-resistant tuberculosis[13] recommendations were also reviewed for any changes. As was the updated joint guideline from the CDC, Infectious Disease Society of America (IDSA), and National Institute of Health (NIH) for treatment of opportunistic infections in HIV patients[14]. Updated treatment guidelines from the IDSA were also evaluated for bacterial rhino-sinusitis[15]; community acquired pneumonia[16]; management of intra-abdominal infections[17]; urinary tract infection from catheters[18]; febrile neutropenia[19]; and acute uncomplicated cystitis and pyleonephritis[20]. No changes regarding the use of fluoroquinolones were found.

Recommendations:
- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

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3. Shah, V. M. *et al.* Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers. *Cornea* **29**, 751–757 (2010).
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6. Safety Information > Factive (gemifloxacin mesylate) Tablet. at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm279846.htm>
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17. Solomkin, J. S. *et al.* Diagnosis and Management of Complicated Intra- abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clinical Infectious Diseases* **50**, 133–164 (2010).
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Appendix 1

Randomized Clinical Trial Article Abstracts

Judlin, P. *et al.* Efficacy and safety of moxifloxacin in uncomplicated pelvic inflammatory disease: the MONALISA study. *BJOG: An International Journal of Obstetrics & Gynaecology* 117, 1475–1484 (2010).

Objective**:** To evaluate the efficacy and safety of moxifloxacin versus levofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease (uPID) in Asia.

Design: Prospective, randomised, double-blind, double-dummy, parallel-group study.

Setting: Multicentre, multinational study in the inpatient and/or outpatient setting.

Population**:** Women (aged ≥18 years) with uPID (defined as PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination) and not requiring intravenous treatment.

Methods**:** Women received a 14-day course of either oral moxifloxacin, 400 mg once daily, or oral levofloxacin, 500 mg once daily, plus oral metronidazole, 500 mg twice daily. Additionally, a single dose of ceftriaxone, 250 mg intramuscularly, was administered to women who had a positive screening test for *Neisseria gonorrhoeae*.

Main outcome measures**:** The primary measure of efficacy was clinical response at test-of-cure (TOC) (7–14 days after the last dose of study drug) in the per-protocol population. Noninferiority of moxifloxacin to the comparator regimen was demonstrated if lower limit of 95% CI was >−15%. Other measures were clinical response during therapy and at 4-week follow up, microbiological response at TOC, and safety.

Results: A total of 460 women were randomised to the study. For the primary measure of efficacy (clinical cure at TOC), moxifloxacin was noninferior to levofloxacin plus metronidazole (moxifloxacin: 152/194, 78.4%; comparator 155/190, 81.6%; 95% CI −10.7 to +4.9). The most commonly isolated pathogens at baseline included *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Escherichia coli*, *Staphylococcus aureus*, *Peptostreptococcus* spp., *Proteus mirabilis*, *Streptococcus agalactiae* and *Klebsiella pneumoniae*. Bacteriological success rates were high and comparable between treatment arms (microbiologically valid populations, moxifloxacin 27/30, 90.0%; comparator 22/26, 84.6%; 95% CI −12.7 to +20.3). Both treatments were well tolerated.

Conclusions: Moxifloxacin monotherapy, 400 mg once daily for 14 days, is an effective and well-tolerated oral treatment for women with uPID.

Heystek, M. & Ross, J. D. C. A randomized double-blind comparison of moxifloxacin and doxycycline/metronidazole/ciprofloxacin in the treatment of acute, uncomplicated pelvic inflammatory disease. *Int J STD AIDS* 20, 690–695 (2009).

This multicentre, double-blind study was undertaken to demonstrate non-inferiority of once-daily oral moxifloxacin compared with combination therapy in the management of acute, uncomplicated pelvic inflammatory disease (PID). Women aged ≥18 years with PID were randomized to receive moxifloxacin (400 mg once daily) for 14 days or comparator treatment (doxycycline [100 mg twice daily] plus metronidazole [400 mg three times daily] for 14 days, plus one single 500-mg ciprofloxacin dose). Of the 434 valid per protocol (PP) patients, the overall clinical success rates at 2–14 days post-therapy were 96.6% (moxifloxacin) and 98.0% (comparator); moxifloxacin was non-inferior to the comparator regimen both in the PP (95% confidence interval [CI]: −4.5, 1.6) and intent-to-treat (95% CI: −5.8, 6.9) populations. Clinical success rates at 21–35 days post-therapy were 93.8% (166/177; data missing for 47 patients) for moxifloxacin and 91.3% (147/161; data missing for 37 patients) for the comparator. Bacteriological success rates at 2–14 days post-therapy were 92.5% (moxifloxacin) and 88.2% (comparator). Once-daily dosing and proven efficacy suggest that moxifloxacin may be of value in acute, uncomplicated PID.

Marom, T. *et al.* Comparison of safety and efficacy of foam-based versus solution-based ciprofloxacin for acute otitis externa. *Otolaryngol Head Neck Surg* 143, 492–499 (2010).

Objective**:** To compare and evaluate the efficacy and safety of a foam-based antibiotic formulation in the treatment of acute otitis externa (AOE) with the more conventional solution-based formulation.

Study Design**:** Phase 2, open-label, randomized controlled trial. Setting**:** Multicenter. Subjects and methods: Sixty-three eligible adult patients with unilateral AOE were randomly assigned to one of two treatment groups: an experimental 0.3 percent foam-based ciprofloxacin, (FoamOtic Cipro) or 0.3 percent solution-based ciprofloxacin (Ciloxan). All patients received the same dose regime (twice daily for 7 days). The primary efficacy variable was response to therapy (cure) in the test-of-cure visit. Secondary variables included improvement of the disease symptoms otalgia, tenderness, edema, and otorrhea.

Results: Sixty-four patients were enrolled in the study. Seven patients were excluded from the per-protocol analysis due to major deviations from the protocol. Per-protocol analysis (n = 57) showed that cure was achieved in all the patients (P = 1.000). No significant differences were found between groups for symptomatic relief, resolution of otic discharge, or onset of pain reduction. Both treatments were found to be highly efficacious and safe, demonstrating the noninferiority of the experimental drug.

Conclusion: Foam-based ciprofloxacin is a safe and an effective new treatment for AOE.

Appendix 2

Abstracts for Meta Analyses

Rafalsky, V. V., Andreeva, I. V. & Rjabkova, E. L. Quinolones for uncomplicated acute cystitis in women. *Cochrane Database of Systematic Reviews* (2006).at <http://doi.wiley.com/10.1002/14651858.CD003597.pub2>

Background: Fluoroquinolones are sometimes used to treat multiple-drug-resistant and drug-sensitive tuberculosis. The effects of fluoroquinolones in tuberculosis regimens need to be assessed.

Objectives: To assess fluoroquinolones as additional or substitute components to antituberculous drug regimens for drug-sensitive and drug resistant tuberculosis.

Search methods: In July 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, LILACS, Science Citation Index, Database of Russian Publications, and *meta*Register of Controlled Trials. We also scanned reference lists of all identified studies and contacted researchers.

Selection criteria: Randomized controlled trials of antituberculous regimens containing fluoroquinolones in people diagnosed with bacteriologically positive (sputum smear or culture) pulmonary tuberculosis.

Data collection and analysis: Two authors independently applied inclusion criteria, assessed the risk of bias in the trials, and extracted data. We used risk ratio (RR) for dichotomous data, mean difference (MD) for continuous data (both with 95% confidence intervals (CI)), and the random-effects model if we detected heterogeneity and it was appropriate to combine data.

Main results: Eleven trials (1514 participants) met the inclusion criteria. No statistically significant difference was found in trials substituting ciprofloxacin, ofloxacin or moxifloxacin for first-line drugs in relation to cure (416 participants, 3 trials), treatment failure (388 participants, 3 trials), or clinical or radiological improvement (216 participants, 2 trials). Substituting ciprofloxacin into first-line regimens in drug-sensitive tuberculosis led to a higher incidence of relapse (RR 7.17, 95% CI 1.33 to 38.58; 384 participants, 3 trials) and longer time to sputum culture conversion (MD 0.50 months, 95% CI 0.18 to 0.82; 168 participants, 1 trial), although this was confined to HIV-positive participants. Substituting for ethambutol in first-line regimens led to a higher incidence of total number of adverse events (RR 1.34, 95% CI 1.05 to 1.72; 492 participants, 2 trials). Adding or substituting levofloxacin to basic regimens in drug-resistant areas had no effect. A comparison of sparfloxacin versus ofloxacin added to regimens showed no statistically significant difference in cure (184 participants, 2 trials), treatment failure (149 participants, 2 trials), or the total number of adverse events (253 participants, 3 trials).

Authors' conclusions: Only ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin and moxifloxacin have been tested in randomized controlled trials for treating tuberculosis. We cannot recommend ciprofloxacin in treating tuberculosis. Trials of newer fluoroquinolones for treating tuberculosis are needed and are ongoing. No difference has been demonstrated between sparfloxacin and ofloxacin in drug-resistant tuberculosis.

Ziganshina, L. E. & Squire, S. B. Fluoroquinolones for treating tuberculosis. *Cochrane Database of Systematic Reviews* (2008).at <http://doi.wiley.com/10.1002/14651858.CD004795.pub3>

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