

ID Pearl: Dangers of Fluoroquinolones in Uncomplicated Infections

Intended Audience: Physicians, Pharmacists, and allied health providers

Background:

- Over 33 million treatment courses of oral fluoroquinolones (FQ) are administered annually, of which 10 million are for the 3 indications covered in this ID pearl
 - 9.32 million are for uncomplicated urinary tract infections (UTI), 795K for acute bacterial sinusitis (ABS), and 216K for acute bacterial exacerbation of chronic bronchitis (ABECB) in patients with COPD
- On July 26, 2016, an FDA MedWatch Drug Safety Communication was sent out stating that health care professionals should not prescribe systemic FQ to patients who have other treatment options for **acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated UTI** because the risks outweigh the benefits
- This recommendation was based on data from an FDA safety review, which has shown that systemic use of FQ is associated with disabling and potentially permanent serious side effects that can occur together¹
- Major side effects associated with FQ use include: neurological side effects, joint and muscle pain, tendonitis and tendon rupture, exacerbation of Myasthenia Gravis, and QT prolongation
- In 1996, all quinolones were required to have a Black Box Warning for tendinitis and tendon ruptures
- In July 2016, the FDA revised the Boxed Warning to address these other serious safety issues
- Although diarrhea is not commonly reported with FQ use, patients are at a greater risk for developing community and hospital-acquired *C. difficile*, including the highly virulent BI/NAP1 strain of *C. difficile*²

Patients at risk for FQ adverse events:

- Elderly patients:
 - An increase in age is associated with changes in drug absorption, distribution, and renal function (excretion)³
 - Geriatric patients are at increased risk for developing severe tendon disorders
 - Elderly patients may be more susceptible to drug associated effects on QT prolongation
- Pregnant women:
 - FQ are pregnancy category C and their use in pregnant women is cautioned

Side Effects/ Warnings:

- Neurological side effects:
 - Occurs in 1-2% of patients
 - 2nd most common adverse event in FQ²
 - Side effects include seizures, dizziness, hallucinations, headaches, confusion and peripheral neuropathy
 - Elderly are the highest group at risk
- Tendonitis/tendon rupture:
 - Tendinopathy is a class-wide effect
 - Older age (> 60 years), concomitant corticosteroid therapy, presence of renal dysfunction, and history of solid organ transplant are all potential risk factors for tendinopathy³
 - Symptom onset varies considerably, studies report an average onset of 9–13 days after FQ therapy initiation (range 1 to 152 days)³
 - Results from a database study by Wise et al found that the use of quinolones was strongly associated with an increased risk of Achilles tendonitis (OR=4.3, 95% CI: 3.2–5.7) and tendon rupture (OR=2.0, 95% CI: 1.2–3.3)⁴
- QT prolongation:
 - QT prolongation is a class-wide effect: Moxifloxacin>Levofloxacin>Ciprofloxacin
 - Patients are at risk for developing torsade de pointes and sudden cardiac arrest
 - A cohort study by Lapi., et al, concluded moxifloxacin and ciprofloxacin were associated with elevated rates of serious arrhythmia (RR=3.30; 95% CI, 1.47-7.37 and RR=2.15; 95% CI, 1.34-3.46, respectively)⁵
 - This study looked at over 600,000 patients receiving FQ from 1990-2005, and a total of 1838 arrhythmias were observed in patients (4.7/100,000 person years), of which 34% of patients had a fatal arrhythmia

Fluoroquinolone Restrictions

Condition	Management
Acute Sinusitis	<p>90 – 98% of rhinosinusitis cases are viral & diagnosis is based on symptoms⁶</p> <p>Diagnose acute bacterial rhinosinusitis based on symptoms that are:</p> <ul style="list-style-type: none"> ○ Severe (>3-4 days), such as a fever $\geq 102^{\circ}\text{F}$ and purulent nasal discharge or facial pain ○ Persistent (>10 days) without improvement, such as nasal discharge or daytime cough ○ Worsening (3-4 days) such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement of a viral upper respiratory infections (URI) lasting 5-6 days <p>If a bacterial infection is established:</p> <ul style="list-style-type: none"> ○ Watchful waiting is encouraged for uncomplicated cases for which follow up is available: <p>Medication recommendations:</p> <ul style="list-style-type: none"> ○ Amoxicillin/clavulanate is the recommended 1st line therapy ○ Macrolides are not recommended due to high levels of <i>Streptococcus pneumoniae</i> antibiotic resistance (~40% in Sarasota Community) ○ For penicillin-allergic patients' doxycycline is a recommended alternative <p>Antibiotic recommendation:</p> <ul style="list-style-type: none"> ○ Amoxicillin/clavulanate 875/125 mg po BID or 500/125 mg po TID ○ Doxycycline 100mg PO BID or 200mg po daily <p>Sinus radiographs are not routinely recommended</p>
Acute Bronchitis	<p>Acute bronchitis is primarily a viral illness and routine treatment with antibiotics is not justified and vigorous efforts to curtail their use should be encouraged</p> <ul style="list-style-type: none"> ○ Colored sputum does not indicate bacterial infection <p>Evaluation should focus on ruling out pneumonia, which is rare among otherwise healthy adults in the absence of abnormal vital signs (RR ≥ 24 bpm, oral temp $\geq 38^{\circ}\text{C}$ & abnormal lung findings)⁴</p> <p>Routine treatment of uncomplicated acute bronchitis with antibiotic is not recommended, regardless of cough duration.</p> <p>Options for symptomatic therapy include:</p> <ul style="list-style-type: none"> ○ Cough suppressants (codeine, dextromethorphan) ○ First generation antihistamines (diphenhydramine) ○ Decongestants (phenylephrine) and beta agonists (albuterol)
Uncomplicated UTI	<p>Classic symptoms include dysuria, frequent voiding of small volumes and urinary urgency. Hematuria and suprapubic discomfort are less common⁴</p> <p>For uncomplicated cystitis in healthy adult, non-pregnant, premenopausal women:</p> <p>Preferred regimen:</p> <ul style="list-style-type: none"> ○ PO outpatient: Nitrofurantoin 100 mg BID x 5 days ○ IV inpatient: Cefazolin 1 gram q8h x 5-7 days <p>Alternative therapy:</p> <ul style="list-style-type: none"> ○ PO outpatient: Cephalexin 500 mg q8h x 5-7 days ○ IV inpatient: Ceftriaxone 1 gram IV q24h x 5-7 days ○ Bactrim 160/800 mg BID x 3 days (avoid for empiric therapy if possible as <i>E. coli</i> resistance in Sarasota County exceeds 20%)

Summary:

- Due to the risks of serious adverse drug events, the FDA has advised that the risk of using a fluoroquinolone outweighs the benefits for patients with uncomplicated cystitis, acute sinusitis and acute bronchitis who have other treatment options
- Serious adverse outcomes of FQ use include *C. difficile* infections, neurological side effects, tendon rupture, joint and muscle pain, QT prolongation, acute exacerbation of Myasthenia Gravis, hypersensitivity, and cardiac arrhythmias
- The risks versus benefits of the use in FQ in specific patient population must be considered, as safer alternatives are usually available

References:

1. FDA MedWatch - Fluoroquinolone Antibacterial Drugs for Systemic Use: Drug Safety Communication - Warnings Updated Due to Disabling Side Effects. 07-26-2016.
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2. Duke Antimicrobial Stewardship Outreach Network (DASON). The dangers of Fluoroquinolone use: FDA weighs in.
https://dason.medicine.duke.edu/sites/dason.medicine.duke.edu/files/june_2016_dason_newsletter-fluoroquinolones_final.pdf
3. Bidell MR et al. Fluoroquinolone-Associated Tendinopathy: Does Levofloxacin Pose the Greatest Risk? *Pharmacotherapy*, 2016 Jun;36(6):679-93
4. Wise, B.L., et al., Impact of age, sex, obesity, and steroid use on quinolone-associated tendon disorders. *Am J Med*, 2012. 125(12): p. 1228 e23-1228 e28
5. Lapi, F., et al., Fluoroquinolones and the risk of serious arrhythmia: a population-based study. *Clin Infect Dis*, 2012. 55(11): p. 1457-65
6. CDC's Get Smart program website: Get Smart Resources for Healthcare Providers:
<http://www.cdc.gov/getsmart/week/educational-resources/hcp.html>

Prepared by: Vilna Roberts, PharmD Candidate

Reviewed by: Jamie Kisgen, PharmD, BCPS (AQ-ID) and Julie Larkin, MD