

DUKE ANTIMICROBIAL STEWARDSHIP OUTREACH NETWORK (DASON)

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The dangers of fluoroquinolone use: FDA weighs in

Antimicrobial stewards have long advocated for avoidance of fluoroquinolones whenever possible due to known risks associated with their use. Now, stewards have even more support for their arguments. On May 12, the Food and Drug Administration (FDA) released [this statement](#) regarding the risk of fluoroquinolone use for uncomplicated infections. The FDA recommended restricting fluoroquinolone use in uncomplicated urinary tract infections, bronchitis, and sinusitis. In DASON hospitals in 2015, fluoroquinolones represented the third (levofloxacin 10.5% of DOT) and eighth (ciprofloxacin 3.6% of DOT) most commonly used antibiotic agents. Thus, reducing the use of fluoroquinolones is a key target for DASON hospitals. This newsletter will review the major adverse effects of fluoroquinolones and discuss alternative agents for uncomplicated infectious syndromes commonly treated with fluoroquinolones.

Fluoroquinolone safety risks

There are four major safety risks with fluoroquinolone use: 1) gastrointestinal side effects, including increased risk of *C. difficile* infection, 2) neurologic side effects including delirium in the elderly, 3) tendonitis and tendon rupture, and 4) QT prolongation, especially with co-administration with other QT prolonging agents. The recent FDA notice only addresses 3 of these risks.

GI side effects and risk of *Clostridium difficile* infection

The most common untoward side effect in patients receiving fluoroquinolones is gastrointestinal disturbance, occurring in 3-17% of patients. Typically, patients experience nausea and vomiting as drug related GI side effects. Antibiotic associated diarrhea from fluoroquinolones is not common. Importantly, however, fluoroquinolone use is a major risk factor for development of community and hospital acquired *C. difficile* infection and also linked with emergence of the highly virulent BI/NAP1 strain of *C. difficile*. Two separate meta analyses report odds ratios (OR) of 5.50 (95% CI, 4.26 to 7.11) [1] and 5.65 (95% CI 4.38-7.28) [2] for fluoroquinolone related community onset *Clostridium difficile* colitis. Many hospitals struggle with prevention of *C. difficile* infection, thus targeting reductions in fluoroquinolone use as a stewardship initiative is a key focus for hospital ASPs.

Neurologic side effects

Neurologic side effects are the second most common adverse event of fluoroquinolone use. These side effects are dizziness, headache, confusion, hallucinations, and peripheral neuropathy. Elderly patients are the highest risk group due to their overall susceptibility to development of delirium and problems with

polypharmacy. The most common neurologic side effect is dizziness, and occurred in 11% of patients in one study (ref). Overall, neurologic side effects occur in 0.9-11% of patients taking fluoroquinolones (ref). Fluoroquinolones should not be used in patients with myasthenia given the drug class' neuromuscular blockade activity.

Tendonitis and tendon rupture

Although a rare side effect (less than 1%), fluoroquinolones can cause highly morbid conditions of tendonitis and even tendon rupture. This is, indeed, a black box warning on all fluoroquinolones. Wise et al. conducted a database study of over 6 million people who received fluoroquinolones. The authors identified 28,907 incident cases of Achilles tendonitis and 7685 incident cases of tendon rupture [3]. They also evaluated for antibiotic exposure (fluoroquinolones, amoxicillin, nitrofurantoin) 30 days prior to diagnosis. Fluoroquinolone use was associated with an increased risk of Achilles tendonitis (267 patients out of 28,907 patients had tendonitis and concurrent fluoroquinolone use, odds ratio [OR], 4.3; 95% confidence interval [CI], 3.2-5.7). Quinolone use was also associated with tendon rupture (48 patients out of 7685 patients had tendon rupture and concurrent fluoroquinolone use, OR, 2.0; 95% CI, 1.2-3.3). The other antibiotics included in the analysis had no association with tendonitis or tendon rupture [3]. Patients placed on fluoroquinolones should be warned to notify their provider if they develop tendon pain so that early discontinuation of the agent can avoid progression to tendon rupture.

QT prolongation

All fluoroquinolones may prolong the QT interval. A prolonged QT interval places the patient at risk for polymorphic ventricular tachycardia (PVT), also known as torsades des pointes and sudden cardiac death. Lapi et al. evaluated the number of arrhythmias in a nested case control study of over 600,000 patients receiving fluoroquinolones from 1990-2005[4]. The authors observed a total of 1838 arrhythmias (incidence rate of 4.7/100,000 person-years). Fatal arrhythmias occurred in 629 (34%) out of 1838 patients with arrhythmias. Serious arrhythmias were associated with fluoroquinolone use and the relative risk was 1.76 (95% CI 1.19-2.59). Moxifloxacin and ciprofloxacin were associated with serious arrhythmias, with relative risks (RR) of 3.30 (95% CI 1.47-7.37) and 2.15 (95% CI 1.34-3.46) respectively. Contrastingly, Ray et al compared the risk of sudden cardiac death in patients receiving amoxicillin versus ciprofloxacin and found no difference. The authors also compared the risk of sudden cardiac death in patients receiving amoxicillin versus levofloxacin and found a non-significant increased risk of cardiac death with levofloxacin (hazard ratio, 1.50; 95% CI, 0.82 to 2.72; P=0.18) [5]. The observational data cited above is conflicting due to limitations in study design, so no firm conclusions can be made on if one quinolone agent is "worse" for QT prolongation than others. The QT prolonging effect is directly observable in clinical practice when QT is monitored during quinolone therapy. Avoidance of fluoroquinolones is most important when greater than one QT prolonging agent is used, in patients who already have borderline or long QT intervals, and in patients with existing significant cardiac disease.

Infectious syndromes and alternatives to avoid fluoroquinolones

The FDA outlined three clinical scenarios where clinicians should avoid prescribing fluoroquinolones: 1) uncomplicated cystitis, 2) sinusitis, and 3) bronchitis. Additionally, we question whether antibiotics should be prescribed at all for the aforementioned syndromes. Below, we review each syndrome, indications for antibiotic therapy, and alternative agents to fluoroquinolone use.

Acute Uncomplicated Cystitis

DASON recommends therapy for patients **with dysuria** and laboratory evidence of urinary tract infection (UTI) (pyuria on good quality urinalysis, $\geq 10^5$ colony forming units/mL of bacteria on urine culture). Patients without symptoms, regardless of laboratory evidence, should not be treated with antibiotics unless the patient is pregnant or undergoing a urologic procedure that will breach the urethral mucosal barrier [6].

For female patients who have acute dysuria and laboratory evidence of a UTI, appropriate empiric antibiotic recommendations are: 1) nitrofurantoin 100mg twice daily for 5 days, 2) trimethoprim-sulfamethoxazole (TMP-SMX) 1 double strength tablet twice daily for 3 days, or 3) fosfomycin 3 grams once [7].

Acute Sinusitis

The majority of acute sinusitis cases are viral, and therefore, antibiotics have no role in treatment. Patients who have **persistent or worsening** symptoms 10 days after onset of upper respiratory, purulent nasal discharge, and facial pain symptoms may benefit from antibiotic therapy. Most acute viral sinusitis syndromes do not resolve after 10 days, therefore a patient who has improved but is still symptomatic after 10 days of illness should not receive antibiotics. IDSA recommends amoxicillin-clavulanate as first line therapy for acute bacterial sinusitis. Patients with penicillin allergies may receive doxycycline as an alternative agent [8].

Acute Bronchitis

Viral infections cause most cases of acute bronchitis. Despite this, 60-90% of patient receive antibiotics for acute bronchitis [9]! Moreover, patients who receive antibiotics for acute bronchitis are more likely to have untoward effects from the antibiotics than benefit. Antibiotics should not be prescribed for a patient with acute bronchitis without evidence of pneumonia. However, the patient should receive symptom management with cough suppressants, expectorants, and antihistamines. [9] For patients with COPD flare, an alternative agent is azithromycin.

Take Home Points

1. Reduction in fluoroquinolone use is a key target for hospital ASPs.
2. Fluoroquinolones can lead to serious adverse outcomes: *C. difficile* infection, neurologic side effects, tendonitis/tendon rupture, and death from cardiac arrhythmia.
3. Uncomplicated urinary tract infections can be effectively treated with alternative agents.
4. Viral infections commonly cause acute sinusitis and bronchitis, and empiric antibiotic therapy is generally not warranted in those conditions. If antibiotics are indicated, alternative agents to fluoroquinolones should be used.

References

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