Joint Meeting of the Antimicrobial Drugs and Drug Safety and Risk Management Advisory Committees

Benefits, Overprescribing and Safety of Systemic Fluoroquinolones
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Testimony of Sidney M. Wolfe MD
Victoria Powell MD

Public Citizen's Health Research Group

We have no financial conflict of interest

Restatement of Three Discussion Questions

- For each of three diseases, ABS (acute bacterial sinusitis), ABECB-COPD (Acute bacterial exacerbation of chronic bronchitis in patients with COPD) and uUTI (uncomplicated urinary tract infection), discuss unique treatment effects and estimated overprescribing of fluoroquinolones

- Discuss safety information, especially in the context of needed label strengthening, including black box warnings, that might reduce overprescribing by clarifying the higher risk/benefit ratio. *Safety label changes would be identical for all indications*

Acute bacterial exacerbation of chronic bronchitis (ABECB-COPD)

FQ indication: Mod – severe exacerbation of SEVERE COPD (FEV1<50% predicted), hospitalization ≤90 days ago, ≥4 antibiotics in last year, systemic steroid use, or prior sputum culture growing pseudomonas*

For broadly defined ABECB-COPD in 2014, levofloxacin was second most commonly used antibiotic [23.3%] and ciprofloxacin 5th [6.6%] [FDA Briefing Document p. 36, table 16]. This almost certainly represents overuse/inappropriate use of these drugs.

*Infect Dis Clin North Am. 2004 Dec;18(4):861-82, ix. doi:10.1016/j.idc.2004.07.006

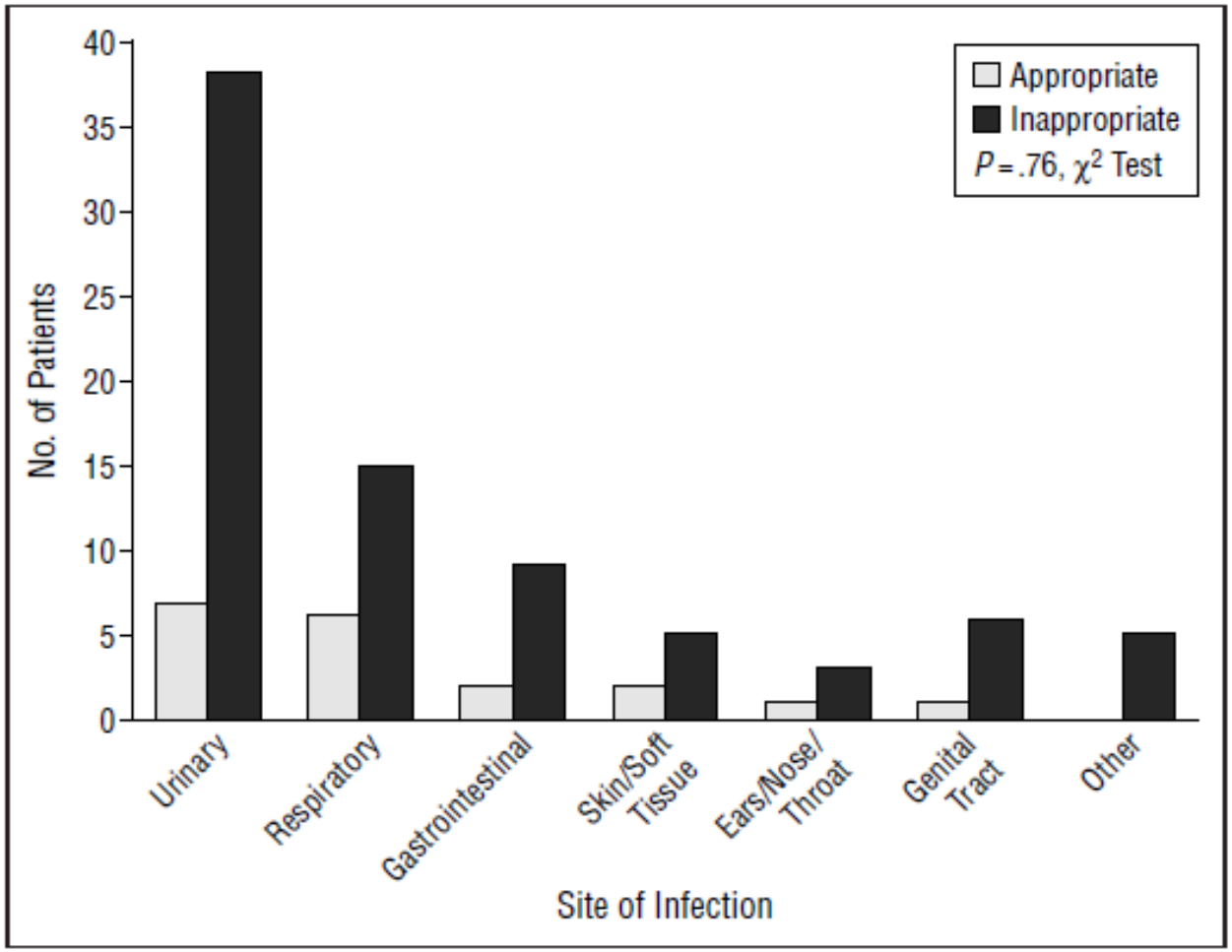
Uncomplicated Urinary Tract Infection

IDSA 2010 guidelines DO NOT include quinolones as first line therapy.*

Examining the pattern of use, for broadly defined uUTI from office based surveys, ciprofloxacin is the most commonly used antibiotic (32.3%); levofloxacin 5th most common (4.9%). This almost certainly represents overuse.**

* *Clin Infect Dis*. 2011;52(5):e103-e120.doi:10.1093/cid/ciq257.

** Encuity Treatment Answers ™ with Pain, 2010&2014, Extracted AUG2014, Source File(s): PDDA 2015-896 FQ AC AUG2015 [from FDA Briefing Document p. 37 table 18]



Appropriateness of fluoroquinolone use by site of infection.

Two academic medical centers studied 100 consecutive ED patients receiving a FQ and subsequently discharged. Appropriateness of the indication for use was judged according to existing institutional guidelines. *Arch Intern Med*:163, March 10, 2003 (The Chi-squared analysis shows no variation in inappropriate Rx among infection sites.)

Other findings from ED Study

- FQs accounted for approximately 25% of all antibiotics prescribed
- 81% of FQ prescriptions were inappropriate
- 43 (53%) were considered inappropriate because another agent was considered first line (most often sulfamethoxazole- trimethoprim for UTIs in patients not allergic to sulfa)
- 27 (33%) were inappropriate because there was no evidence of infection based on the clinical evaluation or diagnostic studies.
- In 11 (14%) there was insufficient evaluation.

"The impact of arrhythmogenic effects on the risk-benefit balance for nonserious infections needs to be considered."*.

"Some fluoroquinolones, including LEVAQUIN®, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia". (current Levaquin label)-similar for Avelox

- "We found that the incidence of tendinitis/tendon rupture among fluoroquinolone-exposed persons ranged from 1.3 to 5.6 per 10,000 [13 to 56 per 100,00] person-years and the incidence of cardiac arrhythmias ranged between 15-57 per 100,000 patients exposed to fluoroquinolones. Both adverse events are infrequent but appeared to be higher in comparison to unexposed persons or persons exposed to a different antibacterial drug."**

*Mosholder Memo, PDF page 176

**FDA Briefing, PDF page 17

Conclusions

- Significant overprescribing exist for FQs
- Warnings buried in the label are not likely to be noticed or heeded
- As recommend by FDA reviewer Dr. Andrew Mosholder, a black box warning (BBW) for the well documented QTc prolonging effects of FQ is needed. We would add to the BBW the risk of excess arrhythmias, often a consequence of prolonged QTc. “Compounds which prolong the QTc interval in a concentration-dependent manner can increase serious arrhythmias, especially in a vulnerable population.”*
- Evidence for this is on a par with evidence leading to a FQ BBW for tendinopathy and myasthenia gravis.

*Mosholder Memo, PDF page 192