
Pharmacotherapy Conference
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OBJECTIVES

1. Identify fluoroquinolone (FQ) resistance trends, specifically: Acinetobacte spp., Escherichia coli (E. coli), Klebsiella spp., and Pseudomonas spp.
2. Understand the impact of Gram-negative resistance on the pharmacokinetics (PK) and pharmacodynamics (PD) of the fluoroquinolones
3. Speculate as to the potential consequences of fluoroquinolone resistance
1. Introduction

- The fluoroquinolone (FQ) class of antibiotics was first discovered in the 1960’s after the accidental discovery of nalidixic acid as a by-product of the anti-malarial agent chloroquine
- Norfloxacin was the first fluoroquinolone approved by the Food and Drug Administration (FDA) in 1984
- Early fluoroquinolones had good aerobic Gram-negative coverage, but were not very active against aerobic, gram positive bacteria or anaerobic Gram-negative bacteria
- After chemical structure alteration, the 2nd generation of fluoroquinolones was created
- The second generation of fluoroquinolones added aerobic Gram-positive bacterial coverage and better Gram-negative coverage
- The respiratory fluoroquinolones, like levofloxacin and moxifloxacin, added enhanced coverage against the Gram-positive organism Staphylococcus pneumoniae
- The FQ’s exert their antimicrobial effect by inhibition of bacterial topoisomerase II (also known as DNA gyrase) and topoisomerase IV
- Inhibition of these enzymes prevents the coiling and transcription of bacterial DNA, leading to cell death¹
- After becoming available for use in the mid-1980’s, fluoroquinolones quickly became one of the most prescribed antibiotic classes between 1995 and 2002²
  - Prescribing more than tripled from 7 million in 1995 to 22 million in 2002
  - 58% of prescribing was for FDA approved diagnoses: UTI, sinusitis, lower respiratory tract infection
  - 42% was for diagnoses not approved by FDA: acute bronchitis, otitis media, acute upper respiratory tract infection

Potential reasons for increased FQ prescribing:

- Broad spectrum of coverage, particularly useful for diseases like community acquired pneumonia (CAP)
- Enhanced Staphylococcus pneumoniae activity with the respiratory fluoroquinolones
- Rapid adoption as first line therapies in clinical practice guidelines³, ⁴

CAP indications: Outpatients with comorbidities
- Inpatient double-coverage for Pseudomonas spp.

HAP/VAP indications: Early onset, no multi-drug resistant (MDR) risk factors
- Double-coverage for Pseudomonas spp
Table 1: The Fluoroquinolones

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
<th>Coverage</th>
<th>MOA</th>
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<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Broad spectrum (Gram positive,</td>
<td>Inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Gram-negative, atypicals)</td>
<td></td>
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<tr>
<td>Moxifloxacin</td>
<td></td>
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<tr>
<td>Gatifloxacin</td>
<td></td>
<td></td>
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<tr>
<td>Gemifloxacin</td>
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</tbody>
</table>

Collateral Damage

- The human body is home to hundreds of different species of bacteria, both beneficial and pathogenic, including Gram-negative and Gram-positive organisms
- Antimicrobials lack the ability to differentiate between the body’s normal flora and the pathogenic organism
- Broad spectrum antibiotics expose both target and “innocent by-stander” bacteria to the effects of the antibiotic
- Exposure to antibiotics and incomplete suppression of bystander bacteria can lead to resistance; this may lead to a poor response to antimicrobial therapy during the next exposure.

National and International Awareness

International

- In 1998, the World Health Organization (WHO) began issuing resolutions related to antimicrobial resistance
- In 2001, WHO published the WHO Global Strategy for Containment of Antimicrobial Resistance
- This statement focuses on patient and provider education, curbing inappropriate antimicrobial use, encouraging the surveillance of resistant organisms and antimicrobial use

United States

- In 1999, the Center for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Institutes of Health (NIH), and 7 other federal agencies came together to form the Interagency Task Force on Antimicrobial Resistance
- In 2001, the Interagency Task Force on Antimicrobial Resistance released its “Public Health Action Plan to Combat Antimicrobial Resistance”
- The plan is broken down into four focus areas: surveillance, prevention and control, research, and product development
- Multiple grants have been developed to fund antimicrobial surveillance, appropriate antibiotic prescribing education, mechanism of resistance research, product development, and increasing vaccine availability
2. Critical Evaluation of Relevant Literature

PIES or PIER Criteria

<table>
<thead>
<tr>
<th><strong>Patient population</strong></th>
<th>Are there any major differences in patient characteristics that may confound the results? Evaluate the inclusion/exclusion criteria: they serve as a guide to the patients for whom the study results may be applicable.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Is the intervention being tested representative of current practice or derived from previous well-conducted studies?</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>Do the endpoints of the trial truly represent what is claimed as being studied? Is the endpoint used in the trial clinically significant? If a surrogate endpoint is used, is it validated for correlation to a hard clinical endpoint?</td>
</tr>
<tr>
<td><strong>Statistics or Results</strong></td>
<td>Statistical tests appropriate? Is the effect size clinically relevant? NNT? Are the results significant? Are the results applicable?</td>
</tr>
</tbody>
</table>

Table adapted from Baroletti S, et al. *Crit Pathways in Cardiol*. 2004;3: 205-8

Correlation of FQ use and resistance
Neuhauser MM et al. *JAMA*. 2003;289(7):885-8

| **Patient population** | • 77-117 ICU’s for 43 states tested ≥ 100 consecutive Gram-negative aerobic isolates recovered from patients each year from 1994-2000  
• Mostly respiratory isolates (51.5%), which were mostly *Pseudomonas* (31.6%) |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Intervention** | • Susceptibility testing using standardized MIC panel  
• Clinical and Laboratory Standards Institute (CLSI) methods were used |
| **Endpoints** | • Gram-negative isolates susceptibilities to selected antimicrobials |
| **Results** | • Ciprofloxacin susceptibility decreased 10% from 1994-2000  
• 13% decrease in *Pseudomonas* susceptibility to ciprofloxacin compared to previous study done from 1990-1993 \(^{10}\)  
• Decline in ciprofloxacin susceptibility was significantly associated with increasing national use of fluoroquinolones during the study period |
Correlation of FQ use and resistance (cont)
Neuhauser MM et al. JAMA. 2003;289(7):885-8

Figure 1: Fluoroquinolone Use and Resistance Rates in Pseudomonas aeruginosa and Gram-negative Bacilli
Figure adapted from Neuhauser MM et al. JAMA. 2003;289(7):885-8

Limitations:
- Does not provide any information as to how hospitals were selected, other than that Merck representatives queried hospitals in the US
- Confounders not taken into account: prior antibiotic exposure, hospital/ICU length of stay, +/- mechanical ventilation
- FQ usage data not derived from the patients who produced the isolates that were tested

3. Fluoroquinolone PK/PD

Table 2: Fluoroquinolone PK/PD

<table>
<thead>
<tr>
<th>Type of killing</th>
<th>Concentration dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic (PK) /Pharmacodynamic (PD) Index</td>
<td>Area under the concentration curve (AUC)/Mean inhibitory concentration (MIC) Goal : $\geq 125$</td>
</tr>
<tr>
<td>Post Antibiotic Effect (PAE)</td>
<td>$\geq 2$hrs</td>
</tr>
</tbody>
</table>
Fluoroquinolone PK/PD (cont)

Table 1: Clinical Laboratory and Standards Institute (CLSI) Breakpoints:

<table>
<thead>
<tr>
<th></th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter sp., E.coli, Klebsiella sp., Pseudomonas sp.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
</tr>
</tbody>
</table>


Terminology

**Monte Carlo Simulation**

- Mathematical technique for predicting outcomes using random sampling within pre-defined distributions
- Model generates possible outcomes for a given scenario
- Useful for predicting outcomes that are influenced by many different variables

- In infectious disease research, these variables include PK information, like area under the concentration curve (AUC), and microbiological information like mean inhibitory concentration (MIC)

**Probability of Target Attainment (PTA)**:

- The probability that a specific value of a PK/PD index is achieved or exceeded at a certain MIC

**Cumulative Fraction of Response (CFR)**:

- The proportion of the studied population achieving a certain PK/PD index using a Monte Carlo simulation given the MIC's of the organisms studied

PTA

100 patient sample

MIC = 1 (fixed MIC)

AUC/MIC target: ≥125

65 patients reach ≥ 125

PTA = 65 at an MIC of 1

CFR

100 patient sample

10 different MIC’s

Goal AUC/MIC: ≥125

80 patients reach ≥ 125, for this collection of MICs

CFR = 80% for this collection of MICs
### Setting the AUC/MIC standard


<table>
<thead>
<tr>
<th>Patient population</th>
<th>74 patients, obtained from 3 open-label clinical trials performed using ciprofloxacin in the 5 years prior to this study: 2 Lower respiratory tract infection (LRTI) studies, 1 Pseudomonas and <em>S. aureus</em> infection study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Mostly ICU, average age 68 (range 24-91)</td>
</tr>
<tr>
<td></td>
<td>• Mostly LRTI patients (58 LRTI, 9 wound/soft tissue infections, 4 bacteremias, 3 complicated urinary tract infections)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Ciprofloxacin 200mg IV Q12H: 41 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Ciprofloxacin 400mg IV Q8H: 24 patients</td>
</tr>
<tr>
<td></td>
<td>• Ciprofloxacin 300mg IV Q12H: 8 patients</td>
</tr>
<tr>
<td></td>
<td>• Ciprofloxacin 400mg IV Q12H: 1 patient</td>
</tr>
<tr>
<td></td>
<td>• Infused over 1 hour</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Clinical cure: resolution of all signs and symptoms, continued stable signs upon discontinuation of antibiotic therapy, and no need for treatment of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Microbiological failure: persistence of the organism, regardless of whether or not it acquired resistance</td>
</tr>
<tr>
<td></td>
<td>• Time to bacterial eradication: duration of treatment to the treatment day that the culture first became negative and remained negative upon repeat culture</td>
</tr>
<tr>
<td></td>
<td>• 66 patients evaluable for this outcome</td>
</tr>
<tr>
<td></td>
<td>• 64 patients evaluable for this outcome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>After analyzing the probability of both clinical and microbiologic cure, Forrest et al observed the highest cure percentages were seen in the 125 to 250 AUC/MIC range group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Significantly worse outcome in both clinical (42% cure below 125, 82% cure above 125, <em>P</em> &lt;0.005) and microbiologic (26% cure below 125, 82% cure above 125, <em>P</em> &lt;0.001) outcomes seen when AUC/MIC ratio was less than 125</td>
</tr>
<tr>
<td></td>
<td>• MIC's above 0.25 were significantly worse for clinical and microbiologic cures.</td>
</tr>
<tr>
<td></td>
<td>• Time to eradication: significant difference (<em>P</em> &lt; 0.005)</td>
</tr>
<tr>
<td></td>
<td>• AUC/MIC of &lt; 125: average 32 days (however only 30% of pts in this group actually had eradication)</td>
</tr>
<tr>
<td></td>
<td>• AUC/MIC 125-250: average 6.6 days</td>
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<tr>
<td></td>
<td>• AUC/MIC &gt;250: average 1.9 days (note, there was no improvement in eradication time with AUC/MIC much greater than 250 when the &gt;250 group was analyzed)</td>
</tr>
<tr>
<td></td>
<td>• Multivariate analysis: AUC/MIC most significant variable for probability of both clinical and microbiological outcomes</td>
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<tr>
<td></td>
<td>• AUC/MIC below 125 was significantly predictive of both clinical (<em>P</em> = 0.0027) and microbiologic failure (<em>P</em> = 0.0001)</td>
</tr>
</tbody>
</table>
Setting the AUC/MIC standard (cont)
Forrest A et al. *Antimicrob Agents Chemother.* 1993;37(5):1073-81\(^{12,13}\)

<table>
<thead>
<tr>
<th>AUC/MIC Range</th>
<th>Total no. of patients</th>
<th>Clinical Cure</th>
<th>Microbiological Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of patients</td>
<td>%</td>
</tr>
<tr>
<td>0 – 62.5</td>
<td>9</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>62.5 – 125</td>
<td>10</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>125 – 250</td>
<td>16</td>
<td>14</td>
<td>88</td>
</tr>
<tr>
<td>250 – 500</td>
<td>7</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>500 – 5541</td>
<td>22</td>
<td>17</td>
<td>77</td>
</tr>
</tbody>
</table>

Table adapted from Forrest A et al. *Antimicrob Agents Chemother.* 1993;37(5):1073-81

Limitations:

- Not told why those particular doses were selected; was it trial protocol or were they adjusted for renal function? (average CrCl: 63ml/min, range 17-151ml/min, ciprofloxacin requires adjustment at 50 ml/min\(^{14}\))
- Concomitant medications given in some patients: rifampin in five *S. aureus* infected patients, azlocillin in six *Pseudomonas* sp. infected patients
- Gram positive infections included in case mix (eleven *S. aureus* patients)
- Site of infection is not uniform; may confound results
- PK/PD data is only from patients obtained from two of the clinical trials, does not contain the patients obtained from the second LRTI study\(^{13}\) (used one LRTI study and one *Pseudomonas* and *S. aureus* infection study)
Impact of emerging Gram-negative resistance on the PK/PD of the FQ’s
Crandon et al. Ann Pharmacother.2009;43:220-7\textsuperscript{15,16}

| Patient population | • 5000 patient Monte Carlo simulation  
| | • Pharmacokinetic data obtained from population pharmacokinetic studies  
| | o Ciprofloxacin data obtained from Forrest et al study above  
| | o Levofloxacin data from 30 critically ill adults receiving 250mg or 500mg IV Q24H, mostly LRTI, mostly gram-negative, but some \textit{S. pneumoniae} and \textit{S. aureus} isolated\textsuperscript{16}  
| | • MIC data obtained from 2002, 2004, and 2006 Meropenem Yearly Susceptibility Test Information Collection (MYSTIC)  
| Intervention | • Simulated 30 minute infusions of one of 10 different antibiotics, including:  
| | o Levofloxacin 750mg Q24H  
| | o Ciprofloxacin 400mg IV Q8H  
| | o Ciprofloxacin 400mg IV Q12H  
| Endpoints | • CFR  
| | o Optimal CFR considered to be 90% or greater  

Results

- FQ’s demonstrated suboptimal CFR’s regardless of dose or pathogen  
- 20.3% decrease in \textit{E. coli} CFR from 2002 to 2006  
- Of all antimicrobials and regimens tested, FQ’s displayed the lowest CFR’s to \textit{Pseudomonas}  
- Authors caution against the use of FQ’s as monotherapy when \textit{E. coli} is a suspected pathogen

| Table 3: Cumulative Fraction of Response (%) of Standard Dosing Regimens |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Antimicrobial   | Dosing Regimen  | \textit{Escherichia coli} |          | \textit{Klebsiella spp} |          | \textit{Pseudomonas aeruginosa} |          |
| Ciprofloxacin   | 400mg Q12H | 91.6 | 78.3 | 71.3 | 93.6 | 91.3 | 79.8 | 62.1 | 61.1 | 63.5 |
| Ciprofloxacin   | 400mg Q8H | 92.1 | 78.6 | 71.8 | 95.6 | 92.8 | 80.9 | 65.6 | 65.5 | 67.0 |
| \textbf{Susceptibility to Ciprofloxacin (%)} | | 92.9 | 78.9 | 72.3 | 98.1 | 94.7 | 81.9 | 72.3 | 74.8 | 73.9 |
| Levofloxacin    | 750mg Q24H | 78.6 | 72.1 | 91.8 | 80.4 | 52.9 | 55.8 |
| \textbf{Susceptibility to Levofloxacin (%)} | | 79 | 72.8 | 95 | 82.7 | 70.6 | 71.8 |

Table adapted from Crandon et al. Ann Pharmacother.2009;43:220-7
**Impact of emerging Gram-negative resistance on the PK/PD of the FQ’s (cont)**

**Limitations:**
- Ciprofloxacin data obtained from Forrest et al study above, same limitations (see above)
- Levofloxacin data limitations: patients recieved 250mg or 500mg IV Q24H, not 750mg Q24H simulated in this study
- Some *S. pneumoniae* and *S. aureus* infections included
- MYSTIC database used only represents 15 US hospitals
- Hospitals contributing to MYSTIC database changed over the 5 year study period, may have had an impact on susceptibilities
- Excluded renally impaired, obese, non-ICU, and malignancy patients, limiting applicability to ICU patients without renal failure

**Should the AUC/MIC threshold be increased for patients with bloodstream infections (BSI) due to Gram-negative bacteria?**

<table>
<thead>
<tr>
<th>Patient population</th>
<th>178 BSI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 42 cases evaluable for PK/PD analysis</td>
<td></td>
</tr>
<tr>
<td>• Enterobacteriaceae BSI, mostly community acquired infections (62.9%)</td>
<td></td>
</tr>
<tr>
<td>• Some patients received concurrent β-lactam therapy</td>
<td></td>
</tr>
<tr>
<td>• 24.2% of patients required ICU admission</td>
<td></td>
</tr>
<tr>
<td>• <em>E. coli</em> was predominate pathogen (62.4%)</td>
<td></td>
</tr>
<tr>
<td>• Isolates also obtained from urinary tract in 50.6% of patients and intrabdominal wounds in 25.8% of patients</td>
<td></td>
</tr>
<tr>
<td>• Average age of 66 years</td>
<td></td>
</tr>
<tr>
<td>• Isolate data:</td>
<td></td>
</tr>
<tr>
<td>o 167 (93.8%) susceptible per CSLI standards (MIC ≤ 1mg/L)</td>
<td></td>
</tr>
<tr>
<td>o 2 (1.1%) intermediate (MIC = 2)</td>
<td></td>
</tr>
<tr>
<td>o 9 (5.1%) resistant (MIC ≥ 4)</td>
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</tr>
</tbody>
</table>

**PK/PD analysis:** 42 patients who received ciprofloxacin within 24hrs of positive blood culture
- 70% *E. coli* infections
- 18 (42.9%) received concurrent β-lactam therapy
- Mostly female (73.8%)

**Monte Carlo Simulation patients:** 5000 simulated patients
- Used ‘real patient’ data (CrCl: 61.5 ± 42ml/min and body weight: 72.4 ± 17.1kg)
- PK data obtained from Forrest et al PK study in critically ill patients (see above)

**Intervention**
- Simulated infusions of one of the following regimens:
  - Ciprofloxacin 200mg IV Q12H (low dose)
  - Ciprofloxacin 400mg IV Q12H (standard dose)
  - Ciprofloxacin 400mg IV Q8H (high dose)
    - Doses reduced at CrCl < 30ml/min per manufacturer recommendations
      (CrCl: 5-29ml/min 250mg -500mg Q18H, dialysis: 250-500mg Q24H after dialysis)

**Endpoints**
- Cumulative target attainment (CTA): identical to CFR
- Clinical cure: resolution of infection-related signs and symptoms without relapse
- Treatment failure: fever ≥ 38°C or positive blood culture exceeding 72 hours, or relapse of either

**Results**
- Clinical cure documented in 133 patients (74.7%) of all cases
- **PK/PD Analysis:** 42 patients
  - 34 (81%) had documented clinical cure
  - Factors significantly associated with treatment failure:
    - Low AUC/MIC ($P = <0.0001$), high MIC ($P = 0.001$), male gender
Results (cont)

- Multivariate analysis using male gender as comparator:
  - Low AUC/MIC ($P = 0.012$) and high MIC ($P = 0.019$) still significant
- Multivariate analysis excluding ciprofloxacin resistant isolates:
  - AUC/MIC still significant ($P = 0.038$), MIC no longer significant ($P = 0.78$)
- AUC/MIC breakpoint of 250 most significant
  - AUC/MIC >250 cure rate 91.4% vs AUC/MIC < 250 cure rate 28.6% ($P = 0.001$)
- AUC/MIC 125 breakpoint vs AUC/MIC 250 breakpoint:
  - >125: 84.2% cure, <125: 50% ($P = 0.16$)
  - >250: 91.4% cure, <250: 28.6% ($P = 0.001$)

- **Monte Carlo Simulation**: 5000 simulated patients
  - Probability of achieving AUC/MIC ≥ 250:
    - Ciprofloxacin 200mg IV Q12H (low dose): 0.85
    - Ciprofloxacin 400mg IV Q12H (standard): 0.88
    - Ciprofloxacin 400mg IV Q8H (high dose): 0.89

---

**Light grey**: Clinical cure  
**Black**: Treatment failure

![Figure 10](image1.png)  
**Figure 10**: Clinical cure and failure by AUC/MIC

![Figure 11](image2.png)  
**Figure 11**: AUC/MIC, AUC, and MIC stratified by treatment response

Should the AUC/MIC threshold be increased for patients with bloodstream infections (BSI) due to Gram-negative bacteria? (cont)

Limitations:
• Small sample size for PK/PD evaluation
• Only BSI patients, limits applicability to other infection sites
• Concurrent β-lactam therapy; 42.9% of PK/PD patient subset

4. What can be done to curb FQ resistance?

Is fluoroquinolone restriction the answer?

| Patient population | • Members of the Clalit Health Services HMO living in the Sharon district of central Israel, approximately 167,000 patients
|                    | • 19,570 urine cultures positive for E. coli from January 2000 – July 2004
|                    | • 95% from females
|                    | • 28% from elderly patients

| Intervention       | • 3 phases:
|                    |   o Preintervention period: January 2000 – October 2001: 22 months
|                    |   o Intervention period: November 2001 – May 2002: 7 months
|                    |   • Nationwide restriction on ciprofloxacin use; preapproval by authorized head of clinics was required for all ciprofloxacin prescriptions
|                    |   o Postintervention period: June 2002 – July 2004: 26 months
|                    |   • Restriction never formally waived, but generic ofloxacin introduced to HMO formulary, resulting in increased FQ use

| Endpoints          | • FQ consumption
|                    | • E. coli urine isolates susceptibility to FQ’s

| Results            | • Number specimens from which E. coli was isolated increased during study period
|                    | • Overall increase in FQ use in study period, but significant decrease in use during intervention period ($P < 0.001$)
|                    | • 25% decrease in E. coli non-susceptibility to FQ’s: 12% preintervention vs 9% intervention ($P = 0.014$)
|                    | • Significant difference in inverse relationship between FQ use and E. coli FQ susceptibility ($P = 0.001$)
|                    | • 36% reduction in non-susceptibility between months of highest FQ use (8321 defined daily doses, DDDs, per month) and months of lowest FQ use (4027 DDDs per month)
|                    | • Amoxicillin-clavulanate and cefuroxime use increased over time
|                    | • No change in E. coli susceptibility to either of these antimicrobials was observed

Limitations:
• Low applicability to male patients
• E. coli “non-susceptibility” not defined
• Only ciprofloxacin restricted (it did, however account for 90% of FQ use leading up to this study)
• Community study limits applicability to inpatients, ICU patients
5. Conclusions
   • Fluoroquinolone use has risen dramatically since the introduction of these antibiotics
   • Gram-negative fluoroquinolone resistance is apparent on both the local and national levels
   • PK/PD targets may need to be updated in the setting of Gram-negative BSI
   • Fluoroquinolone restriction may be an effective measure to curb resistance
References