Goodbye excessive Fluoroquinolone use, hello decreased *C. difficile* rates

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Objectives

1) Describe the link between fluoroquinolone use and *C. difficile* infection (CDI)
2) Discuss strategies to decrease unnecessary use of fluoroquinolones as an antimicrobial stewardship initiative
3) Propose beta-lactam allergy management as a fluoroquinolone reduction strategy
Decreasing inappropriate use of fluoroquinolones is one of the most important interventions that a stewardship program can make for *C. difficile* reduction.

The primary risk factor for nosocomial CDI is antibiotic exposure

All Antibiotics Are Not Created Equal

Clindamycin

3rd Generation Cephalosporins

Fluoroquinolones


NAP1/BI/027

- Hypervirulent strain capable of producing higher levels of Toxin A & Toxin B
- High-level fluoroquinolone resistance
- Associated with:
  - Greater odds of severe disease (aOR 1.74; 95% CI, 1.36-2.22)
  - Severe outcomes (aOR 1.66; 95% CI, 1.09-2.54)
  - 14-day mortality (aOR 2.12; 95% CI, 1.22-3.68)

Are fluoroquinolones associated with CDI?

Does reducing fluoroquinolone use reduce CDI rates?


Ok, stop we get it

UMMC Internal Data

Are fluoroquinolones associated with CDI?

Does reducing fluoroquinolone use reduce CDI rates?

How can I reduce fluoroquinolone use at my institution?
Antimicrobial Stewardship Strategies

- Front end: Formulary restriction and preauthorization
- Back end: Interventions after antimicrobials have been prescribed
- BOTH: Prospective audit with intervention and feedback

Supplemental Strategies

- Education, guidelines, clinical pathways
- Dose optimization via PK-PD
- De-escalation/Streamlining
- Combination therapy
- Antimicrobial order forms/order sets if CPOE
- IV-PO switch
- Computerized decision support
- Antimicrobial cycling

Auditing/Feedback

- Examples
  - Review all patients on fluoroquinolones and recommend alternatives as appropriate
  - Utilize institution specific data to identify target service areas or prescribers with higher fluoroquinolone use for review

References:
- Dellit TH, et al. CID 2007;44:159-77
- Barlam T, et al. CID 2016;62:e51-77
- Virulence 2013;4:151-157
Auditing/Feedback

<table>
<thead>
<tr>
<th>Pros</th>
</tr>
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<tbody>
<tr>
<td>• Adaptable to many hospital environments</td>
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<tr>
<td>• Can be done a few times a week versus daily</td>
</tr>
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<td>• Can intervene in cases of inadequate therapy</td>
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<td>• Facilitates a team approach to patient care</td>
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<td>• Has been shown to improve antimicrobial use and outcomes</td>
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<td>• Provides educational opportunities</td>
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<td>• More easily accepted by physicians than restrictions/pre-authorization</td>
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<table>
<thead>
<tr>
<th>Cons</th>
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<tbody>
<tr>
<td>• Can be labor intensive</td>
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<tr>
<td>• Success depends on the effectiveness and skill of staff making the interventions</td>
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<td>• For maximal efficiency requires systems to identify patients to intervene on and how to best convey suggestions</td>
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Restrictions/Pre-authorization

• **Examples**
  • Mandating ID consults or stewardship approval for fluoroquinolones
  • Specific requirements that must be met for dispensing of fluoroquinolones (‘checklist’)

Restrictions/Pre-authorizations

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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</table>
| • Effective in decreasing targeted antibiotics  
• Can influenced future prescribing practices – education built into the process of discussing therapy choice | • May shift prescribing to alternative agents  
• May be less acceptable to prescribers (loss of prescriber autonomy)  
• May delay time to therapy for patients  
• Effectiveness depends on skills of staff making recommendations and reviewing requests |

Guideline Changes

<table>
<thead>
<tr>
<th>Indication</th>
<th>Fluoroquinolone Substitution</th>
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<tbody>
<tr>
<td>Bronchitis</td>
<td>No antibiotics! If truly indicated, doxycycline</td>
</tr>
</tbody>
</table>
| Infective Exacerbation of COPD – non-severe | Doxycycline  
Amoxicillin/Clavulanate |
| Community Acquired Pneumonia | Ampicillin/Sulbactam + Azithromycin  
Ceftriaxone + Azithromycin |
| Urinary Tract Infection – Cystitis | Nitrofurantoin |
| Urinary Tract Infection – Pyelonephritis | SMX/TMP |
| Intra-abdominal Infections | Ceftriaxone +/- Metronidazole  
Piperacillin/tazobactam (if Pseudomonas coverage needed) |
Leverage the Electronic Medical Record (EMR)

- Remove fluoroquinolones from ordersets
- Build warning alert about the toxicities

Mang N, et al. ID Week 2018

Leverage the Electronic Medical Record (EMR)

- Suppress reporting of fluoroquinolone susceptibilities from the microbiology lab

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Organism: Escherichia coli</th>
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</thead>
<tbody>
<tr>
<td>AMIKACIN</td>
<td>&lt;=2 S</td>
</tr>
<tr>
<td>AMPICILLIN</td>
<td>&gt;32 R</td>
</tr>
<tr>
<td>AMPICILLIN/SULBACTAM</td>
<td>&lt;=2 S</td>
</tr>
<tr>
<td>CEFAZOLIN</td>
<td>&gt;32 R</td>
</tr>
<tr>
<td>CEFTRIAZONE</td>
<td>&lt;=2 S</td>
</tr>
<tr>
<td>NITROFURANTIN</td>
<td>&gt;32 S</td>
</tr>
<tr>
<td>PIPERACILLIN/TAZOBACTAM</td>
<td>&lt;= 4 S</td>
</tr>
<tr>
<td>TRIMETHOPRIM/SULFAMETHOXAZOLE</td>
<td>&lt;= 20 S</td>
</tr>
</tbody>
</table>

Urine Culture: >100,000 CFU E. coli
Goodbye Fluoroquinolones!

THE ROLE OF ALLERGIES
PCN Allergy – How common

- PCN & other beta-lactams are the most frequent cause of medication-induced anaphylaxis
- Up to 10% of patients report a penicillin allergy
  - Most reports reflect historical childhood events, family history, or non-allergic adverse effects
- Over a 2 year period, 6200 patients admitted to UMMC reported a PCN allergy


PCN Allergy – Overstated?

- Even with a well documented allergy, hypersensitivity may not persist over time due to loss of anti-PCN IgE antibodies (up to 80% over 10 years)
- 9 out of 10 patients who claim to be allergic to penicillin are not truly allergic when assessed by skin testing
- Preferred beta-lactam therapy is avoided in >50% of patients even when a non-severe prior reaction is reported

Implications of PCN “Allergy”

• Increased adverse effects
• Longer hospital stays, more readmissions
  – Approximately one-half day longer
  – 30,000 hospital days/65 million in expenditures
• Development of MDR infections
  – 23.4% increase in *C. difficile* infection
  – 14.1% more MRSA
  – 30.1% increased VRE


Implications of PCN “Allergy”

• Increased usage of broad-spectrum antibiotics
  – FQ, Clindamycin, Vancomycin
• Increased antibiotic costs
  – 63% higher than those without reported allergy
• Antibiotic regimens deviate from standard of care (as defined by national guidelines, protocols or ID consults) in ~40% of patients with a reported PCN allergy

PCN Allergy - Documentation

• Allergy history documentation is poor
  • Often lack documentation of nature and severity of reaction
  • One retrospective cohort found only 39.8% of records had a specific allergen identified and only 22.7% had reaction characteristics identified
  • Appropriate history can improve classification of mild versus life-threatening reactions
  • Rechallenge with beta—lactams is more likely when allergic reactions are well documented


PCN Allergy - Documentation

• Allergy records are rarely updated to demonstrate tolerance
  • ONLY 18% of patients with a documented penicillin allergy who received a penicillin antibiotic without incident had their records updated at UMMC
  • Rarely updated to indicate tolerance of other beta-lactams
  • Algorithms to guide penicillin allergy histories can improve documentation

Oliver WD. JACI In Practice 2017;5:184-6.
Staicu ML. ID Week 2016
PCN Allergy - Documentation

**Question #1: (all)**
What was your reaction to PCN and when did it occur?

- Difficulty breathing, throat closing, tongue/lip/facial swelling
- Don’t Remember
- Rash
- Nausea
- Vomiting
- Diarrhea

Document reaction and when reaction occurred.

**Question #2: (all)**
Have you taken any beta-lactams in the past without a reaction?

- YES
  - Document which beta-lactams patient tolerated. May receive medications in the same class.
- NO
  - Unclear if beta-lactams can be used safely. Consider penicillin skin testing.

Document as a side effect, beta-lactams can be used safely!

**PCN Allergy Documentation**

Rash

**Question #3: (only if rash)**
Was the rash itchy, bumpy, or did skin peel off AND did the rash occur within 1 hour of taking?

- YES
  - Document reaction as severe. If patient has received cephalosporins previously without a reaction, may receive medications in the same class.
- NO
  - Document as low severity. Not a type I reaction. Beta-lactams can be used safely.
Pharmacist Allergy Interviews on FQ Use

Management of Reported Type 1 PCN Allergy

- Desensitization
- Graded Challenges
- Direct Oral Challenges
- Penicillin skin testing
Challenges with Desensitization

• Time consuming
  – Pharmacy preparation
  – Nursing monitoring
• Requires exquisite compliance with antibiotic administration times
• Effects are not sustained

...Wouldn’t it be better to just rule out the allergy?

Direct Oral Challenges

• Administer 250-500 mg dose of amoxicillin and observe for 1 hour after dose
• Reserved for patients with a low suspicion for true anaphylactic allergy (e.g., history of mild childhood rash, nonurticarial rash, adverse events such as nausea or vomiting)
Graded Challenges

- Not intended to induce drug tolerance
- Demonstrates that administration of a specific drug will not result in an immediate reaction
- Give 1%, then 10%, then 100% of therapeutic doses at 30 minute intervals

Antimicrobial Stewardship Guidelines

- Penicillin skin testing is now recommended
- “In patients with a history of β-lactam allergy, we suggest that ASPs promote allergy assessments and PCN skin testing when appropriate”
- Largely unstudied as primary ASP intervention
- Weak recommendation, low-quality evidence
PCN Skin testing (PST)

- PCN & other beta-lactams spontaneously breakdown into reactive intermediates that bind with circulating carrier proteins forming haptens – these serve as the reactive allergenic major and minor determinants for skin testing
- Major determinant – benzylpenicilloyl polylysine accounts for 90% of PCN intermediates
- PST antigens react with IgE antibodies, if present, and the interaction results in a skin wheal, flare, or bleb at the injection site

PCN Skin Testing

- When performed in the appropriate setting with proper technique and reagents, the skin test has a negative predictive value of 97-99% and a positive predictive value of 50%
- Patients with a negative skin test are at no greater risk of experiencing an allergic reaction to a beta-lactam than the general population
Who to test?

• Patients that based on history likely experienced an IgE-mediated allergic reaction
• Patients known to be extremely hypersensitive to penicillin (e.g., systemic or anaphylactic reactions) should not be skin tested
• Ensure patient has not been receiving any histamine blockers (H1 – diphenhydramine and H2 – ranitidine and famotidine) within last 24 hours!!

Models for PST

• Allergy (when available)
• Infectious Diseases Consultants
• Pharmacist-managed (state law dependent)
• Other physician specialties
• Emergency Medicine
• Hospitalist
• **Outpatient/Peri-operative**
WHAT ABOUT OVIVA AND POET?
It’s not all bad….

• Highly bioavailable – facilitate PO option for the treatment of susceptible gram negative bacteremias
• Better bone penetration compared to other agents offering a PO option for the treatment of susceptible pathogens causing osteomyelitis
• Risk of CVCs often outweigh antibiotic risks
• Must weigh patient-specific risks of CDI vs potential benefits of PO FQ administration

Conclusions

• Fluoroquinolones (FQ) are one of the most prescribed antibiotic classes in the US.
• FQs are associated with a high risk of *C. difficile* compared to other classes of antibiotics
• Multiple observational studies have demonstrated reduced *C. difficile* rates through FQ restriction.
• Restriction of FQ is likely to have collateral benefits.
Questions?