AZITHROMYCIN, DOXYCYCLINE, AND FLUOROQUINOLONES

Update in Medicine and Primary Care

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System Antimicrobial Stewardship Pharmacist Manager
OBJECTIVES

1. List three antibiotics that have coverage against atypical respiratory pathogens.
2. Identify which antimicrobial has an extended half-life and how this impacts dosing regimens.
3. Summarize the Food and Drug Administration’s restriction on fluoroquinolones for the treatment of uncomplicated infections.
OVERVIEW

Atypical respiratory bacteria
- *Legionella pneumophila*
- *Chlamydophilia pneumoniae*
- *Mycoplasma pneumoniae*
- *Bordetella pertussis*
- *Coxiella burnetii*

Atypical antibiotic coverage
- Macrolides/ketolides
  - Azithromycin
  - Clarithromycin (think drug interactions)
- Doxycycline
- Fluoroquinolones

20-30% of community-acquired pneumonia, challenging to diagnose

Improved outcomes with atypical coverage for *Legionella*, potentially for others

AZITHROMYCIN

Antibiotic Dosing and Duration (URTI and LRTI)

1500 mg course:
- 500 mg once daily x3 days
- 500 mg on day 1, then 250 mg daily on days 2-5

Clinical Pearl

- Half life: 68 to 72 hours (adults)

Antibiotic Adverse Effects

- Hypersensitivity reactions
- Altered cardiac conduction
- Clostridium difficile
- Drug-resistant bacteria

- Increasing S. pneumoniae resistance
- Nausea, vomiting, and diarrhea

DOXYCYCLINE

Antibiotic Dosing
• 100 mg PO twice daily

Antibiotic Duration
• Typically 7 – 10 days

Clinical Pearl
There are two salt forms: hyclate and monohydrate

Antibiotic Adverse Effects
▪ Tooth and skeletal development
▪ Photosensitivity
▪ Intracranial hypertension
▪ Antianabolic action (incr. BUN)
▪ *Clostridium difficile* (less so)
▪ Drug-resistant bacteria
FLUOROQUINOLONES

Antibiotic Dosing
• Once or twice daily

Antibiotic Duration
• Short courses are well-studied
• E.g., 5 days for pneumonia, 7 days for pyelonephritis

Clinical Pearl
Ciprofloxacin has poor *S. pneumoniae* activity

Adverse Effects – Boxed Warnings
• Tendinitis and tendon rupture
• Central nervous system effects
• Peripheral neuropathy
• Myasthenia gravis exacerbation
• Prolonged QT, Torsades de Pointes
• Phototoxicity
• Hypersensitivity
• Other: *Clostridium difficile*, drug-resistant bacteria, GI intolerance, and more...
## UNDERSTANDING THE DIFFERENT FLUOROQUINOLONES

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Moxifloxacin</th>
<th>Delafloxacin*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em> (i.e., CAP)</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Recently approved; limited clinical data*
FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together

[06-12-2016]

Safety Announcement

The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.
SUMMARY OF EFFICACY

Modest at best:
- Acute bacterial sinusitis
- Mild acute exacerbations of chronic bronchitis (ABECB) in patients with COPD

Likely beneficial, limited data:
- Uncomplicated urinary tract infection

Antibiotics warranted, limited data:
- Moderate-severe ABECB-COPD

Limitations of older “clinical trials”
Sinusitis and ABECB-COPD

Pre-1990
- Not body site specific

1990s
- Non-inferior to these drugs

2000s
- Placebo controlled superiority

COPD: chronic obstructive pulmonary disease
SUMMARY OF SAFETY
FAERS DATABASE REVIEW

Queried the database November 1, 1997 – May 30, 2015

Inclusion Criteria: adverse effects (AEs) in two or more body systems* lasting at least 30 days with a reported outcome of disability in patients who were previously healthy and had received a fluoroquinolone for the three indications discussed in this drug safety communications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and Sex</td>
<td>128 (74%) were 30-59 years old; 138 (78%) were female</td>
</tr>
<tr>
<td>Report type</td>
<td>85% Direct (unusually high)</td>
</tr>
<tr>
<td>Body system</td>
<td>97% musculoskeletal; 69% neuropsychiatric; 63% peripheral nervous system; 32% senses; 15% skin; 12% cardiovascular</td>
</tr>
<tr>
<td>Onset of AEs</td>
<td>Mean: 5.4 days; Median: 3 days; Range: 1 hour – 3 months</td>
</tr>
<tr>
<td>Duration of AEs</td>
<td>Mean: 14 months; Median: 7 months; Range: 1 month – 9 years</td>
</tr>
</tbody>
</table>

FAERS: FDA Adverse Event Reporting System; *peripheral nerves, neuropsychiatric, musculoskeletal, senses, cardiovascular, and skin
CONCLUSION

When prescribing antibiotics, it is important to weigh the benefits and risks of treatment.

Commonly used to cover atypicals in the treatment of respiratory infections:
- Azithromycin
- Doxycycline
- Levofloxacin and moxifloxacin

The risks of fluoroquinolones outweigh the benefits for uncomplicated infections

FDA Review

Any questions?
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# PREFERRED ANTIMICROBIALS (EXTRA SLIDE)

**IDSA/ATS Community-Acquired Pneumonia Guidelines (update in progress)**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Preferred Therapy</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Legionella</em></td>
<td>Fluoroquinolone, macrolide</td>
<td>Doxycycline</td>
</tr>
<tr>
<td><em>Mycoplasma/Chlamydophila pneumonia</em></td>
<td>Macrolide, tetracycline</td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td><em>Coxiella burnetii</em></td>
<td>Tetracycline</td>
<td>Macrolide</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em></td>
<td>Macrolide</td>
<td>TMP/sulfa</td>
</tr>
</tbody>
</table>
The use of antibiotics for the following infections is of questionable benefit:
• Acute bacterial sinusitis
• Mild acute exacerbations of COPD
• Uncomplicated cystitis

While the actual incidence of each adverse reaction is difficult to ascertain, the seriousness of certain uncommon adverse reactions deserves attention:
• Tendonitis/tendon rupture
• Peripheral neuropathy
• Cardiac arrhythmias

The identification of constellations of adverse reactions that appear to be long-term or permanently disabling is a particular concern.

When prescribing antibiotics, it is important to weigh the benefits and risks of treatment.

The risks of fluoroquinolones outweigh the benefits for uncomplicated infections.