Outpatient Antimicrobial Therapy

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Role of Antibacterials in Outpatient Treatment of Respiratory Tract Infection

Vicks VapoRub
Vicks Vapo Rub for Cold Symptoms

- Eligible patients aged 2 to 11 years with symptoms attributed to URIs characterized by cough, congestion, and rhinorrhea that lasted 7 days or longer
- 138 children randomized to Vicks Vapo Rub, petrolatum, or no intervention
- Parents massaged into child’s neck and chest 30 minutes before bedtime


VR, petrolatum, and no treatment on (A) cough frequency, (B) cough severity, (C) severity of congestion, (D) severity of rhinorrhea, (E) child's ability to sleep, (F) parent's ability to sleep, and (G) combined symptom score

Acute Bacterial Rhinosinusitis
What is the treatment of choice for ABRS?

1. Antibacterials
2. Antibacterials + nasal steroids
3. Nasal steroids
4. No antibacterials or nasal steroids

Bacterial Etiology of ABRS

- *S. pneumoniae* 30-35%
  - With 20-30% intermediate and high level resistance to penicillin
- *H. influenzae* 15-25%
  - With 30-40% beta-lactamase producers
- *M. catarrhalis* 5-10%
  - With 99% beta-lactamase producers

Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data

- Searched the Cochrane Central Register of Controlled Trials, Medline, and Embase, and reference lists of reports
- Individual patients' data from 2547 adults in nine trials were checked and re-analyzed

(Lancet 2008; 371: 908)
Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data

- 15 patients with rhinosinusitis-like complaints would have to be given antibiotics before an additional patient was cured
- Patients who were older, reported symptoms for a longer period, or reported more severe symptoms took longer to cure but were no more likely to benefit from antibiotics than other patients

(Lancet 2008; 371: 908)

Antibiotics and Topical Nasal Steroid for Treatment of Acute Maxillary Sinusitis

Double-blind, randomized, placebo-controlled trial of 240 adults with acute sinusitis
Randomized to:
1. Amoxicillin 500 mg TID and nasal steroid
2. Nasal steroid and placebo amoxicillin
3. Amoxicillin and placebo steroids
4. Placebo amoxicillin and placebo steroids

(JAMA 2007; 298: 2487-2496)

Primary Outcome: Proportions of patients with symptoms lasting ≥10 days)

- Amoxicillin: 29/100 (29%)
- No amoxicillin: 36/107 (33.6%)
- Nasal steroid: 32/102 (31.4%)
- No nasal steroid: 33/105 (31.4%)

(JAMA 2007; 298: 2487-96)
What is the treatment of choice for ABRS?

1. Antibacterials
2. Antibacterials + nasal steroids
3. Nasal steroids
4. No antibacterials or nasal steroids

Antibiotics for Chronic Rhinosinusitis

- Prospective, observational study of patients with classic symptoms of CRS undergoing nasal endoscopy and sinus CT
- Patients classified into 2 groups:
  - Radiographic evidence of sinusitis by CT (n=75)
  - Normal CT (n=50)

(Clin Infect Dis 2012; 54: 62)
Endoscopic mucopurulence in patients with CRS confirmed by CT

<table>
<thead>
<tr>
<th></th>
<th>CT+</th>
<th>CT-</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucopurulence</td>
<td>18</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>No mucopurulence</td>
<td>57</td>
<td>50</td>
<td>107</td>
</tr>
<tr>
<td>Subtotal</td>
<td>75</td>
<td>50</td>
<td>125</td>
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</tbody>
</table>

(Clin Infect Dis 2012; 54: 62)

Subjective improvement of antibiotic efficacy

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>CT+ (n=45)</th>
<th>CT- (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>9/45 (20%)</td>
<td>5/26 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement</td>
<td>36/45 (80%)</td>
<td>21/26 (81%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>45/45 (100%)</td>
<td>26/26 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

(Clin Infect Dis 2012; 54: 62)

Acute Otitis Media
What is the drug of choice for acute bacterial otitis media?

1. Azithromycin
2. Amoxicillin-clavulanate
3. Amoxicillin
4. Cefdinir
5. Cefuroxime


- < 6 months of age: give antibacterials for “certain” and “uncertain” diagnosis
- 6 months-2 years: give antibacterials for “certain” diagnosis or severe “uncertain” diagnosis. Use “observation option” for uncertain, non-severe disease
- >2 years: antibacterials for severe certain diagnosis, but observation option for uncertain diagnosis and non-severe certain diagnosis

Otitis Media: AAP/AAFP Recommendations

- Amoxicillin 80-90 mg/Kg/D for 7 days
- Severe disease: amoxicillin-clavulanic acid (90 mg/Kg/D amoxicillin/6.4 mg/Kg/D clavulanic acid)
- Penicillin allergy: cefdinir, cefuroxime, cefpodoxime, ceftriaxone, azithromycin, clarithromycin
- Failure of amoxicillin: amoxicillin-clavulanate, ceftriaxone
Acute Otitis in Children: Post the 2004 Guidelines and the use of PCV7

- Systematic review January 1999-July 2010
- 8945 citations screened, of which 135 citations included
- Tympanic membrane bulging and redness was associated with an accurate diagnosis (JAMA 2010; 304: 2161)

Acute Otitis in Children: Post the 2004 Guidelines and the use of PCV7

- Prevalence of *S. pneumoniae* decreased from 33-48% to 23-31% of isolates and H. influenzae increased from 41-43% to 56-57% post PCV7
- Short-term clinical success higher with amoxicillin/ampicillin than placebo (12% pooled difference)
- Diarrhea and rash more common with amoxicillin (JAMA 2010; 304: 2161)

### S. pneumoniae % resistance (1999-2000)

<table>
<thead>
<tr>
<th></th>
<th>INT</th>
<th>RES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN</td>
<td>12.7</td>
<td>21.5</td>
</tr>
<tr>
<td>AMOX</td>
<td>4.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2.0</td>
<td>25.3</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>2.0</td>
<td>25.7</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>1.4</td>
<td>25.8</td>
</tr>
</tbody>
</table>

(Antimicrob Agents Chemother 2001; 45: 1721)
PCN-I Pneumococcus

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MIC$_{50-90}$ (mg/Kg/D)</th>
<th>Time&gt;MIC (%)</th>
<th>(mcg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Amox 40*</td>
<td>0.25-1.0</td>
<td>55-80</td>
<td></td>
</tr>
<tr>
<td>Cefaclor 40</td>
<td>8-16</td>
<td>0-20</td>
<td></td>
</tr>
<tr>
<td>Cefurox 30</td>
<td>0.5-2.0</td>
<td>40-56</td>
<td></td>
</tr>
<tr>
<td>* 80-100 mg/Kg/day in children</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Clin Infect Dis 1998; 26:1-12)

Pneumococcal Susceptibility

- From the 1999–2000 to the 2004–2005 respiratory illness season:
  - Prevalence of isolates with intermediate penicillin resistance (minimum inhibitory concentration, 0.1–1 µg/mL) increased from 12.7% to 17.9%
  - Prevalence of penicillin-resistant isolates (minimum inhibitory concentration, ≥2 µg/mL) decreased from 21.5% to 14.6%
  - Prevalence of isolates resistant to erythromycin increased from 25.7% to 29.1%
  - The prevalence of multidrug resistance among isolates did not change (22.4% in 1999–2000 and 20.0% in 2004–2005)

(Clin Infect Dis 2010; 48: e23-e33)

Meta-analysis: Macrolide Treatment of AOM

- Included blinded RCTs comparing amoxicillin or amoxicillin-clavulanate to macrolides (azithromycin, clarithromycin) in AOM in children
- Primary outcome: clinical failure measured 10-16 days after starting antibiotics

(Ann Pharmacother 2010; 44: 471-478)
Meta-analysis: Macrolide Treatment of AOM

- 10 trials with 2766 children 15 months to 15 years old included
- Macrolides associated with increased risk of clinical failure (RR 1.31; 95%CI 1.07-1.60; p=0.008)
- Rate of adverse event, particularly diarrhea, significantly less in macrolide group
  (Ann Pharmacother 2010; 44: 471-478)

Acute Otitis Media 2011

- In 1932, AOM and suppurative complications accounted for 27% of all pediatric admissions to Bellevue Hospital
- Today, severe AOM and complications occur, but mostly in children living in regions with limited access to medical care
- It is argued that previous studies were limited due to varying diagnostic criteria and inappropriate antibacterials and dose

AOM in Children <2 Years

- 291 children with AOM diagnosed with strict criteria
  - AOM-SOS scale
  - Middle-ear effusion
  - Moderate to marked bulging of the tympanic membrane or slight bulging accompanied by otalgia or marked erythema of the membrane
- Randomized to amoxicillin-clavulanate (ES) 90 mg/Kg/day or placebo for 10 days
  (NEJM 2011; 364: 105)
AOM in Children <2 Years
• Initial and sustained resolution of symptoms significantly greater with antibiotics
• Rate of clinical failure (persistence of signs of acute infection on otoscopic examination) by Day 5 and Day 12 was significantly less with antibiotics (4%; 16%) compared with placebo (23%; 51%)
• Mastoiditis developed in one child receiving placebo; diarrhea and diaper rash were more common in children receiving antibiotics (NEJM 2011; 364: 105)

AOM in Young Children
• Patients (6-35 months) randomized to amoxicillin-clavulanate 40mg/Kg/D or placebo
  – Pneumatic otoscopic examination with ≥2 of the following: bulging position, ↓ or absent mobility, abnormal color or opacity not due to scarring, or air-fluid interfaces
  – At least one of the following: distinct erythematous patches or streaks or increased vascularity over full, bulging, or yellow tympanic membrane
  – Acute symptoms: fever, pain, respiratory Sx (NEJM 2011; 364: 116)

AOM in Young Children
• Treatment failure: Amox/Clav: 18.6% and Placebo: 44.9%
• Antibiotics ↓ progression to treatment failure by 62% and need for rescue treatment by 81%
• Diarrhea was more common with amox/clav (47.8%) compared to placebo (26.6%)
• Eczema was more common with antibiotics (8.7%) compared with placebo (3.2%) (NEJM 2011; 364: 116)
What is the drug of choice for acute bacterial otitis media?

1. Azithromycin
2. Amoxicillin-clavulanate
3. Amoxicillin
4. “High dose” amoxicillin
5. Cefdinir

Streptococcal Pharyngitis

True or False? Penicillin is the drug of choice in the treatment of pharyngitis due to group A streptococcus.

1. True
2. False
Cephalosporins vs Penicillin for Group A Strep Pharyngitis

• Meta-analysis of 9 randomized, controlled trials in adults
• Odds ratio for bacteriological cure (OR 1.83) and clinical cure rate (OR 2.29) significantly favored cephalosporins (Clin Infect Dis 2004; 38: 1526)

Cephalosporins vs Penicillin for Group A Strep Pharyngitis

• Penicillin is inexpensive, narrow spectrum and well studied in the prevention of rheumatic fever
• Absolute difference between cephalosporins was 5.4%, thus one would need to treat 19 adult patients to see 1 additional bacteriological cure

Streptococcus pyogenes (% Resistance)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0%</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>0%</td>
</tr>
<tr>
<td>Macrolides</td>
<td>6.6-6.9%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.5%</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>0.2%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

Superiority of Cephalosporins over Penicillin in GAS: Mechanism?

- Core tonsillar cultures obtained from 40 children with recurrent tonsillitis treated with either penicillin (PCN) or cefdinir (CEFDN)
- GAS isolated from 11 PCN- and 3 CEFDN-treated patients (p<0.001)
- β-lactamase producing bacteria (S.aureus, H. influenzae, M. catarrhalis) recovered from 17 PCN- and 3 CEFDN-treated patients (p<0.01)
- Inhibiting alpha-hemolytic streptococci were isolated less often from PCN-treated patients than from CEFDN-treated patients


“Expand the pharyngitis paradigm for adolescents and young adults”

- Fusobacterium necrophorum, cause of Lemierre Syndrome, causes pharyngitis in adolescents and young adults with an approximate incidence of 10%
  - GAS: 5 cases of complicated acute rheumatic fever and 1 death per 1,000,000 patients
  - F necrophorum: 20 cases long term disability and 11 deaths per 1,000,000 patients
- Penicillin or a cephalosporin, but not macrolides, are active in vitro


True or False? Penicillin is the drug of choice in the treatment of pharyngitis due to group A streptococcus.

1. True
2. False
Antibacterial Options for Outpatient Treatment of Community Acquired Pneumonia

Etiology Outpatient-Treated CAP (in order of association)

- *S. pneumoniae* (most common organism in older patients and those with significant underlying disease)
- *M. pneumoniae* (most common in patients <50 yo and no co-morbidities)
- *C. pneumoniae*
- Viruses

2007 IDSA/ATS Recommendations: Outpatient Treatment of CAP

- Healthy, no use of antimicrobials within the past 3 months:
  - A macrolide (level I evidence)
  - Doxycycline (level III evidence)
2007 IDSA/ATS
Recommendations: Outpatient Treatment of CAP

• Presence of co-morbidities or receipt of antimicrobials within the past 3 months in which case an alternative from another class should be used:
  – A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, 750 mg levofloxacin): strong recommendation and level I evidence
  – Beta-lactam plus macrolide: level I evidence

2007 IDSA/ATS
Recommendations: Outpatient Treatment of CAP

• “In regions with a high rate (>25%) of infection with high level (≥ 16 mcg/ml) macrolide-resistant *S. pneumoniae*, consider the use of alternative agents.”

Macrolides: Role in Community Acquired Pneumonia
Azithromycin is least likely to be active against which of the following pathogens?

1. Chlamydia pneumoniae
2. Legionella
3. Mycoplasma
4. H. influenzae
5. S. pneumoniae

Pneumococcal Susceptibility

- From the 1999–2000 to the 2004–2005 respiratory illness season:
  - Prevalence of isolates with intermediate penicillin resistance (minimum inhibitory concentration, 0.1–1 µg/mL) increased from 12.7% to 17.9%
  - Prevalence of penicillin-resistant isolates (minimum inhibitory concentration, ≥2 µg/mL) decreased from 21.5% to 14.6%
  - Prevalence of isolates resistant to erythromycin increased from 25.7% to 29.1%
  - The prevalence of multidrug resistance among isolates did not change (22.4% in 1999–2000 and 20.0% in 2004–2005)

  (Clin Infect Dis 2010; 48: e23-e33)

Clinical Relevance of Macrolide-Resistant S. pneumoniae

- Case-control study of patients with bacteremic pneumococcal infection
- Case: organism I or R to erythromycin
- Control: organism S to erythromycin

  (Clin Infect Dis 2002; 35: 556)
Clinical Relevance of Macrolide-Resistant S. pneumoniae

- Receiving macrolides at the time of bacteremia:
  - Cases: 18/76
  - Controls: 0/136
- Patient with M phenotype macrolide resistance:
  - 5/21 patients receiving macrolide
  - 0/40 patients not receiving macrolides

(Macrolides: Gram-negative activity

- Azithromycin/clarithromycin in vitro superiority vs erythromycin against H. influenzae (98-99% of isolates susceptible to doxycycline)
- All agents are adequate in the treatment of Moraxella (but this is not a significant pathogen in most patients)

Macrolides: Other pathogens

- Reliable coverage of atypical pathogens, including Mycoplasma, Chlamydia, Legionella. Respiratory fluoroquinolones and doxycycline also with comparable coverage against these organisms
Macrolides in CAP

- Primary strength is atypical coverage and azithromycin/clarithromycin additionally appear to be adequate in their coverage of *H. influenzae* and *M. catarrhalis*
- Macrolides are unpredictable in pneumococcal susceptibility in certain high risk patients and resistance has been associated with clinical failure; widespread use of macrolides in other indications is contributing to this decline in susceptibility

Macrolide: adverse effects/interactions

- Upper gastrointestinal: less with sustained release products of erythromycin and with azithromycin, clarithromycin
- Otoxicity: dose-related, cochlear, reversible. Risk factors: elderly, renal failure, liver failure

Macrolide: adverse effects/interactions

- Cardiac toxicity: prolonged QT and torsades de pointes. Risk factors: females, underlying cardiac disease
- Drug interactions: erythromycin and clarithromycin potent inhibitors of cyt P 450 with associated increased warfarin, cyclosporine effect; azithromycin has little to no interaction
Pneumococcal Resistance after Cessation of Mass Antibiotic Distributions for Trachoma

- 8 Ethiopian communities received repeated biannual mass azithromycin treatments for trachoma
- After 6 distributions, no additional programmatic treatment for 2 years
- Goal: determine whether selected azithromycin resistance in *S. pneumoniae* persists

(Clin Infect Dis 2010; 51: 571)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Azithromycin resistance</th>
<th>Penicillin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 months (6 months after 4th biannual treatment)</td>
<td>28.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>36 months (6 months after the 6th and final treatment)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>42 months (12 months after the last treatment)</td>
<td>30.0%</td>
<td>0%</td>
</tr>
<tr>
<td>54 months (24 months after the last treatment)</td>
<td>20.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Controls at 24 months</td>
<td>0.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Controls at 36 months</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

(Clin Infect Dis 2010; 51: 571)

Azithromycin Prevention of COPD Exacerbation

- Randomized, placebo-controlled trial of COPD patients with azithromycin 250 mg once daily
- Primary outcome: time to first exacerbation
- Secondary outcomes: quality of life, nasopharyngeal colonization, adherence

Proportion Free of Exacerbations (over 360 days)

Colonylation and Resistance

- Colonization:
  - Azithromycin: 12%
  - Placebo: 31%

- Development of resistance* (%Macrolide resistance in subjects in whom colonization developed during the study and for whom susceptibility testing was performed)
  - Azithromycin: 38/47 (81%)
  - Placebo: 44/108 (41%)
    \( (p<0.001) \)

Association of Antibiotic Prescription and Rate of Penicillin-Nonsusceptible S. pneumoniae

<table>
<thead>
<tr>
<th>Antibiotic prescriptions</th>
<th>1996-2003 (n=25,412) [OR (95%CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1.09 (1.03-1.16)</td>
</tr>
<tr>
<td>Ceftriaxime</td>
<td>1.91 (1.80-2.03)</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>1.91 (1.80-2.03)</td>
</tr>
</tbody>
</table>

(Clin Infect Dis 2011; 53:631)
Association of Antibiotic Prescription and Rate of Multidrug-Nonsusceptible S. pneumoniae

<table>
<thead>
<tr>
<th>Antibiotic prescriptions</th>
<th>1996-2003 (n=25,642) (OR (95%CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1.20 (1.11-1.29)</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>3.13 (2.88-3.39)</td>
</tr>
<tr>
<td>Macrolide</td>
<td>3.13 (2.88-3.39)</td>
</tr>
</tbody>
</table>

(Clin Infect Dis 2011; 53:631)

True or False. Doxycycline is inferior to macrolides with respect to activity versus S. pneumoniae?

1. True
2. False
Doxycycline

- Spectrum of activity is equal to or superior to extended spectrum macrolides vs *S. pneumoniae, H. influenzae, M. catarrhalis*, atypical pathogens
- Twice-daily (once-daily?) dosing regimen results in favorable adherence

*S. pneumoniae* Susceptibility (1999-2002)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood (n=2459)</th>
<th>Pneum (n=1443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>88.4%</td>
<td>76.9%</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>81.9%</td>
<td>73.4%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>92.6%</td>
<td>87.4%</td>
</tr>
<tr>
<td>Penicillin</td>
<td>76.6%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>97.0%</td>
<td>95.8%</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>99.6%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>

(Diagn Microbiol Infect Dis. 2004; 49:147)

Doxycycline

- Almost completely absorbed in the duodenum after oral administration
- Unlike tetracycline, food does not impair absorption (however, concomitant iron and bismuth does)
- Nonrenal clearance
Doxycycline: Adverse Events

- Upper gastrointestinal: nausea, heartburn, epigastric pain, vomiting
- Esophageal ulceration (particularly if administered just prior to bedtime)
- Photosensitivity
- Teeth/bone deposition

Summary: Doxycycline

- Role in outpatient-treated community acquired pneumonia similar to that of the macrolides
  - Same or better spectrum of activity
  - Inexpensive compared to macrolides
  - BID dosing (same as clarithromycin), but advantage to azithromycin
  - Upper GI side effects with both macrolides and doxycycline, but greater incidence of more “severe” upper GI effects with doxycycline

True or False. Doxycycline is inferior to macrolides with respect to activity versus S. pneumoniae?

1. True
2. False
Fluoroquinolones

Respiratory Fluoroquinolone Spectrum of Activity
- Predictable vs beta-lactam and/or macrolide resistant S. pneumoniae
- Outstanding activity vs H. influenzae and M. catarrhalis
- Predictable activity vs atypical pathogens, including Legionella, Chlamydia, Mycoplasma

Quinolone Adverse Effects/Interactions
- Gastrointestinal: 5-10% upper GI; caution with concomitant multivalent cations
- Central nervous system
- Cartilage toxicity in children
- Tendonitis/tendon rupture
Fluoroquinolone Tendonopathy

- FDA has added a boxed warning for all fluoroquinolones
- Incidence: 0.14-0.4%
- Risk highest for patients >60 years and concomitant corticosteroids
  (Med Letter 2008; 50: 93)

Quinolone Adverse Effects

- Prolonged QT: grepafloxacin (withdrawn), moxifloxacin, sparflaxacin (withdrawn). However, most conclude this is a class effect: caution with all quinolones in patients on type 3 agents or with history of prolonged QT
- Hypo/hyperglycemia: gatifloxacin (withdrawn)

Fluoroquinolones and Superinfection
Epidemic, Toxin Gene-Variant Strain of *Clostridium difficile*

- Background: recent reports suggest rate and severity of *C. difficile* disease is increasing
- Total of 187 *C. difficile* isolates between 2000 and 2003 characterized and compared with a database of >6000 isolates from prior to 2001

### Multivariate Antibacterial Risk Factors for *C. difficile*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins</td>
<td>3.8</td>
<td>2.2-6.6</td>
</tr>
<tr>
<td>Quinolones</td>
<td>3.9</td>
<td>2.3-6.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3.3</td>
<td>1.8-5.4</td>
</tr>
<tr>
<td>Most/gatifloxacin</td>
<td>3.4</td>
<td>1.5-7.7</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>0.6</td>
<td>0.2-1.9</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1.6</td>
<td>0.5-4.8</td>
</tr>
<tr>
<td>BLI Comb</td>
<td>1.2</td>
<td>0.7-2.3</td>
</tr>
</tbody>
</table>


### Fluoroquinolones

- Five years ago fluoroquinolones were among those agents (cefepime, penems, aminoglycosides) that could logically be used in the treatment of resistant gram negative infection
- The decline in activity vs Pseudomonas, Enterobacter, and *E. coli*, including ESBL-producers have greatly diminished the role of these agents in the treatment of resistant gram negative pathogens, including *E. coli*
Quinolones in CAP: Pros

- Gemifloxacin, levofloxacin, moxifloxacin cover virtually all suspected pathogens (PCN R S. pneumoniae, H. influenzae, Moraxella catarrhalis, Legionella, Mycoplasma, Chlamydia)
- Once-daily dosing

Quinolones in CAP: Cons

- Quinolones are (were?) active versus multidrug-resistant nosocomial gram-negative organisms.
- Risk factors for the hypervirulent C. difficile
- Does it make sense to use these agents in uncomplicated outpatient infection?

Cost of Oral Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cost</th>
<th>Cost (without insurance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefpodoxime 200 mg q12h</td>
<td>56.20</td>
<td>(68.20)</td>
</tr>
<tr>
<td>Cefuroxime 500 mg q12h</td>
<td>76.20</td>
<td>(143.80)</td>
</tr>
<tr>
<td>Azithromycin (Z-pack)</td>
<td>39.06</td>
<td>(55.20)</td>
</tr>
<tr>
<td>Clarithromycin 500 mg q12h</td>
<td>36.20</td>
<td>(53.30)</td>
</tr>
<tr>
<td>Clarithromycin XL 1 gm q24h</td>
<td>55.50</td>
<td></td>
</tr>
<tr>
<td>Gemifloxacin 320 mg q24h</td>
<td>112.30</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin 750 mg q24h</td>
<td>113.60</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 400 mg q24h</td>
<td>60.50</td>
<td></td>
</tr>
<tr>
<td>Doxycycline 100 mg q12h</td>
<td>11.00</td>
<td>(55.80)</td>
</tr>
<tr>
<td>Amoxicillin 1 g q8h</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate 2 g q12h</td>
<td>67.80</td>
<td></td>
</tr>
</tbody>
</table>
Outpatient-treated CAP: 2009
British Thoracic Society Recommendations

• Nonsevere community-treated CAP:
  Amoxicillin 500 mg PO TID

• Alternatives in those patients unable to tolerate amoxicillin:
  Doxycycline
  Clarithromycin (not azithromycin)

(British Thoracic Society 2009)

Choice of Antibiotic in the Outpatient Treatment of CAP

• Patients with no co-morbidities and not recently exposed to antibacterials:
  – First choice: doxycycline (however, if I lived in the UK, it would be amoxicillin!)
  – Second choice: azithromycin

• “High risk” :
  – First choice: respiratory fluoroquinolone OR combination β-lactam + macrolide/doxycycline