Outpatient Antimicrobial Therapy

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Role of Antibacterials in Outpatient Treatment of Respiratory Tract Infection

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

“An estimated 31 million Americans develop sinusitis each year, leading to 18 million physician visits and $5.8 billion in overall health expenditures.”

American Academy of Allergy, Asthma & Immunology Dec 2008

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
Benefit of Antibiotics for Therapy of Acute Bacterial Rhinosinusitis

The cumulative randomized, double-blind trials suggest that antibiotics are significantly more effective than placebo in decreasing or eliminating symptoms, but the effect is small.

– 81% of those treated and 66% of placebo treated responded at 10-14 days

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)
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)

What is the treatment of choice for ABRS?

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

Management of Acute Otitis Post 2004 Guidelines

• National Ambulatory Medical Care Survey 2002-2006
• 1114 children 6 months-12 years with AOM
• 30 month time periods before and after the guidelines
• Primary outcome: encounter rate at which no antibiotic prescribing was reported

(Pediatrics 2010; 125: 214-220)

Management of Acute Otitis Post 2004 Guidelines

• Rate of AOM encounters in which no antibiotics were prescribed did not change (11%→16%; p=0.103)
• Amoxicillin prescribing increased (40%→49%; p=0.039)
• Amoxicillin-clavulanate prescribing decreased (23%→16%; p=0.043), however cefdinir prescribing increased (7%→14%; p=0.004)

(Pediatrics 2010; 125: 214-220)
Management of Acute Otitis Post 2004 Guidelines

- Rate of analgesic prescribing increased (14%→24%; p=0.038)
- Independent risk factors for an encounter in which antibiotics were not prescribed:
  - Absence of ear pain
  - Absence of reported fever
  - Receipt of an analgesic prescription
    (Pediatrics 2010; 125: 214-220)

S. pneumoniae % resistance (1999-2000)

<table>
<thead>
<tr>
<th></th>
<th>INT</th>
<th>RES</th>
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<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&lt;sub&gt;50-90&lt;/sub&gt; (mg/Kg/D)</th>
<th>Time&gt;MIC (mcg/ml)</th>
<th>(%)</th>
</tr>
</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>
</tbody>
</table>

* 80-100 mg/Kg/day in children
(Clin Infect Dis 1998; 26:1-12)
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)

- 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)
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
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>


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
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

• “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


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

(Clin Infect Dis 2002; 35: 556)

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
- Ototoxicity: 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
True or False. A one week course of clarithromycin or azithromycin results in an increase in macrolide-resistant streptococci lasting for at least six months.

1. True
2. False

Impact of Macrolide Therapy on Pharyngeal Carriage of Macrolide-Resistant Streptococci

- Randomized, double-blind, placebo-controlled trial
- Azithromycin 500 mg QD X 3 days, clarithromycin 500 mg BID X 7 days, or placebo
- Primary outcome: proportion of macrolide-resistant streptococci
- Secondary outcomes: variation in the carriage of macrolide and tetracycline resistance genes and changes in macrolide MIC

(Lancet 2007; 369: 482-490)
Macrolide Resistance
Mechanisms

• Efflux pump (M-type resistance):
  – MICs increase is modest (1-32 mcg/ml)
  – Organism remains susceptible to clindamycin
• Ribosomal methylase (MLS\textsubscript{B}-type resistance):
  – MIC increase is absolute (MIC > 64 mcg/ml)
  – Resistance to (M)acrolides (L)incosamides (S) treptogramins and tetracyclines

Azithromycin vs Clarithromycin:
Impact on Resistance Genes

• Azithromycin had no impact on the rate of carriage of either type of resistance (efflux remained at 85% and ribosomal methylase at 18%)
• Clarithromycin was associated with a significant decrease in carriage of the efflux gene (OR 0.12, 95% CI 0.04-0.32; p<0.0001 at day 8)
• Clarithromycin was associated with a significant increase in carriage of the ribosomal methylase gene (OR 4.75, 95% CI 1.99-11.30; p<0.0004) immediately after clarithromycin use and this persisted even at day 180 (Lancet 2007; 369: 482-490)

True or False. A one week course of clarithromycin or azithromycin results in an increase in macrolide-resistant streptococci lasting for at least six months.

1. True
2. False
Doxycycline

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></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, sparfloxacin (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)

Diplopia and Fluoroquinolones

• Postmarketing surveillance National Registry of Drug-Induced Ocular Side Effects, World Health Organization, FDA
• Possible mechanism: tendinitis of extraocular muscles
• 171 cases (76 men, 91 women, 4 not specified); median age 52 yo
• Median time to appearance of ADR: 9.6 days; 53 positive dechallenge and 5 positive rechallenge (Ophthalmology 2009; 116: 1814-17)

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

- Background: recent reports suggest rate and severity of C. difficile disease is increasing

Multivariate Antibacterial Risk Factors for C. difficile

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporin</td>
<td>3.8</td>
<td>2.2-6.6</td>
</tr>
<tr>
<td>Quinolone</td>
<td>3.9</td>
<td>2.3-6.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3.1</td>
<td>1.8-5.4</td>
</tr>
<tr>
<td>Metronidazol</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>Rifampin Combo</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 (UCSF 2008: 62%), Enterobacter (UCSF 2008: 85-87%), and *E. coli* (UCSF 2008: 63%), 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

- 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
(Cost for 5 days treatment from Wolters Kluwer Health)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cost (3rd party)</th>
<th>Cost (self-pay)</th>
</tr>
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<tbody>
<tr>
<td>Cefpodoxime 200 mg q12h</td>
<td>56.20 (68.20)</td>
<td></td>
</tr>
<tr>
<td>Cefaroxime 500 mg q12h</td>
<td>76.20 (143.80)</td>
<td></td>
</tr>
<tr>
<td>Azithromycin (Z-pack)</td>
<td>39.06 (55.20)</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 500 mg q12h</td>
<td>36.20 (53.30)</td>
<td></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 (55.80)</td>
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</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>
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(Medical Letter 2007; 49: 62-64)

### 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 B-lactam + macrolide/doxycycline