Outpatient Antimicrobial Therapy

B. Joseph Guglielmo, Pharm.D.
Professor and Dean
School of Pharmacy
University of California San Francisco

Disclosures

I have no disclosures regarding conflict of interest
Role of Antibacterials in Outpatient Treatment of Respiratory Tract Infection

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

1. Amoxicillin
2. Amoxicillin-clavulanate
3. Azithromycin
4. No antibacterial therapy

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)
Amoxicillin for Acute Rhinosinusitis

- Randomized placebo controlled trial of adults with uncomplicated, acute RS
- Amoxicillin 500 mg TID or placebo for 10 days
- Symptom improvement:
  - Day 3: Amox (37%); placebo (34%) p=0.67
  - Day 7: Amox (74%); placebo (56%) p=0.02
  - Day 10: Amox (78%); placebo 80%) p=0.71
(JAMA 2012; 307:685-692)

2012 IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis

Clinical presentations which best identify patients with bacterial vs viral (any one)
- Persistent symptoms for ≥ 10 days
- Severe symptoms: fever ≥ 39°C and purulent nasal discharge or facial pain lasting for at least 3-4 consecutive days
- Worsening symptoms ("double sickening")
2012 IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis

Antibacterial choice

– Children: amoxicillin-clavulanate > amoxicillin (strong, moderate recommendation)
– Adults: amoxicillin-clavulanate > amoxicillin (weak, low recommendation)
– Other agents
  • High dose amoxicillin-clavulanate: with severe infection, daycare, age <2 or >65, previous antibacterial use, immunocompromised
  • No fluoroquinolones, macrolides, TMP-SMX, or 2nd and 3rd generation cephalosporins
  • Doxycycline alternative to amoxicillin-clavulanate

Balancing the benefits and risks of empirical antibiotics for sinusitis: A teachable moment

A 70 yo man is diagnosed with acute sinusitis and was treated with an antibiotic. Two days later, he developed diarrhea and discontinued the antibiotic. His physician prescribed Lomotil® for the severe diarrhea.

(JAMA Intern Med E 1-2 (published on line June 2, 2014)
Balancing the benefits and risks of empirical antibiotics for sinusitis: A teachable moment

Five days after the initial visit, he presented to the emergency room pale, low blood pressure, and reporting an “uncountable number of episodes of diarrhea”. He was diagnosed with *Clostridium difficile* infection, developed a toxic megacolon and underwent small bowel resection and near total removal of his large bowel. Despite multiple surgical procedures, mechanical ventilation, and full support, he developed multiorgan failure and ultimately died 17 days after admission.

(JAMA Intern Med E 1-2 (published on line June 2, 2014)

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

S. pneumoniae % Resistance

<table>
<thead>
<tr>
<th></th>
<th>INT</th>
<th>RES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>12.7</td>
<td>21.5</td>
</tr>
<tr>
<td>Amoxicillin</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>
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>
</tr>
</thead>
<tbody>
<tr>
<td>Amox 40*</td>
<td>0.25-1.0</td>
<td>55-80</td>
</tr>
<tr>
<td>Cefaclor 40</td>
<td>8-16</td>
<td>0-20</td>
</tr>
<tr>
<td>Cefurox 30</td>
<td>0.5-2.0</td>
<td>40-56</td>
</tr>
</tbody>
</table>

* 80-100 mg/Kg/day in children

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)
Acute Otitis Media

- 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)
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)
2013 AAP Treatment Guidelines

- Drug of choice: high dose amoxicillin if no purulent conjunctivitis; no penicillin allergy
- If receipt of amoxicillin in the past 30 days or purulent conjunctivitis or history of recurrent AOM unresponsive to amoxicillin: an antibiotic with additional β-lactamase coverage should be prescribed (i.e. amoxicillin-clavulanate), cefdinir, cefuroxime, cefpodoxime)

(Pediatrics 2013; 131: e964 -e999)

Streptococcal Pharyngitis
True or False? Penicillin is the drug of choice in the treatment of bacterial pharyngitis?

1. True
2. False

Streptococcus pyogenes (% Resistance)

- Penicillin: 0%
- Cefdinir: 0%
- Macrolides: 6.6-6.9%
- Clindamycin: 0.5%
- Telithromycin: 0.2%
- Levofloxacin: 0.05%

How Common is Penicillin Allergy?

• 500 patients with medical record history of “penicillin allergy” skin tested with penicilloyl-poly-lysine (Pre-Pen®) and fresh penicillin G
• Negative tests followed by oral amoxicillin challenge
• Four patients reacted with any positive skin tests and another 4 had “significant reactions” to the amoxicillin

(J All Clin Immunol 2013 Feb Abstract 829)

Penicillins and cephalosporins with identical R1 side chains

<table>
<thead>
<tr>
<th>Penicillin</th>
<th>Cephalosporin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Cefoxitin</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Cefaclor Cephalexin</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Cefadroxil Cefprozil</td>
</tr>
</tbody>
</table>

Medical Letter 2012; 54: 101
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
**IDSA 2012 Guidelines Group A Streptococcal Pharyngitis**

- Rapid Antigen Detection Test and/or culture should be performed because clinical features alone do not reliably discriminate between GAS and virus
- Penicillin or amoxicillin for 10 days
- Alternatives: 1st generation cephalosporin (if not “anaphylactically sensitive”), clindamycin, clarithromycin, azithromycin
  
  (Clin Infect Dis 2012; 55: 1279)

**Acute Bronchitis**

A 35 yo man complains of an initially dry and hacking cough, which after a few days, became productive with green mucus. He also complains of fatigue and has a low grade fever (99.5 degrees). His symptoms have continued for 2 weeks.

What is the expected benefit of antibiotic treatment in this patient?
For >40 years, studies have demonstrated that antibiotics are not effective for acute bronchitis (Smith et al. Antibiotics for acute bronchitis. Cochrane Database Syst Rev 2014; 3 (4) CD000245).


Centers for Diseases Control (CDC) efforts have been ongoing to decrease antibiotic prescribing for acute bronchitis. Since 2005, a Healthcare Effectiveness Data and Information Set (HEDIS) measure is that antibiotic prescribing rate for acute bronchitis should be zero.
Antimicrobial Use in Acute Bronchitis

- All patients treated for AB from 1/1-6/30/98 evaluated for initial receipt of antibiotics (n=1842)
- Fall quarter of 1998: patients and physicians provided CDC literature, cough and cold packs, newsletters intended to educate regarding inappropriateness of antibiotics in AB


Antimicrobial Use in Acute Bronchitis

- From 1/1-6/30/99 all patients treated for AB assessed for initial receipt of antibiotics
- Separate geographical clinic site served as control
- Rate of antimicrobial use from respective time periods

Antimicrobial Use in Acute Bronchitis

- 1998: 888/1840 (48.3%) of patients received antibacterials
- 1999: 924/2392 (38.6%) of patients received antibacterials (p<0.001)
- Control site: 142/446 (31.8%) vs 102/321 (31.8%)


Antimicrobial Use in Acute Bronchitis

- Rate of subsequent physician visits was similar (7.9% vs 8.9%) between those initially receiving antibiotics and those that did not
- More patients initially receiving antibiotics required a subsequent antibacterial Rx [45/1812 (2.5%)] compared to those who did not [24/2420 (1.0%)] (p<0.001)

A case of prescription fatigue?
Amoxicillin for acute lower RTI when pneumonia not suspected

- 2061 patients with lower RTI randomized to amoxicillin 1.0 gm TID or placebo for 7 days
- Investigators and patients masked to treatment allocation
- Primary outcome: duration of symptoms rated “moderately bad” or worse
- Secondary outcomes: symptom severity days 2-4 and new or worsening symptoms
  (Lancet Infect Dis Dec 19, 2012)
### Amoxicillin for acute lower RTI when pneumonia not suspected

<table>
<thead>
<tr>
<th>Duration of symptoms moderately bad or worse</th>
<th>Amoxicillin</th>
<th>Placebo</th>
<th>Hazard ratio/Conf intervals/P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[HR 1.06, 95%CI 0.96-1.18; p=0.229]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Mean symptom severity | 1.62 | 1.69 | -0.07 [95% CI -0.15 to 0.007]; p=0.074 |

| New or worsening symptoms | 15.9% | 19.3% | Number needed to treat 30 (16-811) P=0.043 |

| Nausea, rash, diarrhea | 28.7% | 24.0% | Number needed to harm 21, 95% CI 11-174; p=0.025 |

(Lancet Infect Dis Dec 19, 2012)

### 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)

*As of Feb 2015, “Update in Progress”*
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.”
Azithromycin is least likely to be active against which of the following pathogens?

1. Chlamydia
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)

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 azithromycin, clarithromycin compared with erythromycin
- Ototoxicity: dose- and duration-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
Azithromycin and CV Death

• Tennessee patients taking azithromycin, as compared to those who took no antibiotics, had increased risk of CV death (HR 2.88)
• Compared to amoxicillin, azithromycin was associated with increased risk of CV death (HR 2.49)
• Risk of CV death significantly greater with azithromycin compared with ciprofloxacin, but did not differ significantly from levofloxacin

Azithromycin and CV Death: Take 2

• Historical Danish cohort comparing rate of CV death with azithromycin vs no antibiotic Tx; similar comparison of azithromycin vs penicillin
• Risk of death significantly increased with azithromycin compared to no antibiotic, but no difference between azithromycin and penicillin
• Conclusion: Azithromycin not associated with increased risk of CV death
Azithromycin and CV Death: Take 3

- Retrospective cohort comparison of 73,690 veterans ≥ 65yo hospitalized with pneumonia 2007-2012 and prescribed azithromycin versus other guideline-concordant therapy

- 90 day mortality
  - Azithromycin: 17.4%
  - Control: 22.3%

- Myocardial infarction
  - Azithromycin: 5.1%
  - Control: 4.4%

  (JAMA 2014; 311: 2199-2208)

Why ever use clarithromycin?

- Combination of clarithromycin (but not azithromycin) with calcium channel blockers is associated with ↑ risk of hospitalization with kidney injury, ↑ hypotension and ↑ all-cause mortality (JAMA published on line Nov 7, 2013)

- Combination of clarithromycin (or erythromycin) with certain statins associated with ↑ risk for hospitalization due to rhabdomyolysis, kidney injury, and ↑ mortality (Ann Intern Med 2013; 158: 869)

- Increased risk of cardiac death associated with clarithromycin (when compared with roxithromycin) (BMJ Aug 19, 2014)
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

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
  - *Used to be* 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
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
Fluoroquinolones and Superinfection

Multivariate Antibacterial Risk Factors for *C. difficile*

<table>
<thead>
<tr>
<th></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>Moxi/gatifloxacin</td>
<td>3.4</td>
<td>1.5-7.7</td>
</tr>
<tr>
<td>Levofloxacin</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* and MRSA
- Does it make sense to use these agents in uncomplicated outpatient infection?

Quinolone Adverse Events

- Upper GI: nausea, vomiting
- Prolonged QT (like macrolides)
- Dysglycemia: ↑ with quinolones compared with beta-lactams and ↑ risk with moxifloxacin when compared with ciprofloxacin (*Clin Infect Dis* 2013; 57: 971)
- Neuropathy: can occur rapidly and in some patients, the disorder may be permanent. 2013 FDA warning (*Med Lett* 2013; 55: 89)
## Cost of Oral Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefpodoxime 200 mg q12h</td>
<td>56.20 (68.20)</td>
</tr>
<tr>
<td>Cefuroxime 500 mg q12h</td>
<td>76.20 (143.80)</td>
</tr>
<tr>
<td>Azithromycin (Z-pack)</td>
<td>39.06 (55.20)</td>
</tr>
<tr>
<td>Clarithromycin 500 mg q12h</td>
<td>36.20 (53.30)</td>
</tr>
<tr>
<td>Clarithromycin XL 1 gm q24h</td>
<td>55.50</td>
</tr>
<tr>
<td>Gemifloxacin 320 mg q24h</td>
<td>112.30</td>
</tr>
<tr>
<td>Levofoxacin 750 mg q24h</td>
<td>113.60</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg q24h</td>
<td>60.50</td>
</tr>
<tr>
<td>Doxycycline 100 mg q12h</td>
<td>60-120.00!!!!!!</td>
</tr>
<tr>
<td>Amoxicillin 1 g q8h</td>
<td>9.00</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate 2 g q12h</td>
<td>67.80</td>
</tr>
</tbody>
</table>

## Choice of Antibiotic in the Outpatient Treatment of CAP

- Patients with no co-morbidities and not recently exposed to antibacterials:
  - First choice: azithromycin
  - Second choice: doxycycline (if you can afford it!)
- “High risk”:
  - First choice: respiratory fluoroquinolone OR combination B-lactam + azithromycin
Antibiotics and Eczema

- Meta-analysis of observational studies involving children and young adults
- Pooled OR: 1.41 (95%CI 1.30-1.53) associating eczema with antibiotic exposure
- In addition, a 7% increase in eczema risk for each additional antibiotic course received during 1st year of life
  ((Br J Dermatol 2013; 169: 083-991))

Proportion of patients developing IBD and antianaerobic antibacterial status

(P<0.001)

(Pediatrics 2012; 130: e794)
Infant Antibiotic Exposures and Early-Life Body Mass

- Antibiotic exposure during the first 6 months of life associated with significant:
  - Increased body mass
  - Increased weight for length scores
  - Overweight (OR 1.22; p=0.029) at 38 months
    (Intern J Obesity 2012; 1-8)

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-resistant Streptococci After Azithromycin and Clarithromycin

<table>
<thead>
<tr>
<th>Days</th>
<th>Azithromycin</th>
<th>Clarithromycin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>28</td>
<td>70</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>42</td>
<td>90</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>180</td>
<td>120</td>
<td>140</td>
<td>160</td>
</tr>
</tbody>
</table>

Zinc for the common cold

- Meta-analysis RCTs comparing oral zinc with placebo or no treatment
- 17 trials with 2121 participants
- Efficacy
  - 1.65 day ↓ cold symptoms
  - ↓ symptoms in adults but not children
- Adverse events
  - Bad taste: RR 1.65 (95% CI 1.27-2.16)
  - Nausea: RR 1.64 (95% CI 1.19-2.27)
  (Can Med Assoc J 2012; 184: E551-61)
Probiotic and C. difficile: Meta-Analysis

- Twenty trials with 3818 participants
- Probiotics reduced the incidence of CDAD by 66%
- Assuming a 5% incidence of antibiotic-associated CDAD, probiotic prophylaxis would prevent 33 episodes per 1000 patients
- Of probiotic-treated patients, 9.3% experienced ADEs compared with 12.6% in controls

(Ann Intern Med 2012; 157: 878)

Vicks VapoRub
Vicks VapoRub “works”. True or False?

1. True
2. False

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
(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, (G) combined symptom score