Role of Antibacterials in Outpatient Treatment of Upper Respiratory Tract Infection

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)

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 ≥ 102 degrees and purulent nasal discharge or facial pain lasting for at least 3-4 consecutive days
- Worsening symptoms (“double sickening”)
A 1 year old child has been suffering from frequently interrupted sleep, crying upon awakening. She constantly pulls at her left ear and has a fever of 100 degrees.

What is the expected benefit of antibiotic treatment in this patient?

• 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.

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)

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)

- < 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
*Observation option: analgesics and a prescription for amoxicillin to be filled if no improvement in 72 hrs

Streptococcal Pharyngitis

A 23 yo male complains of severe and sudden sore throat without coughing, sneezing, or other cold symptoms. He has difficulty swallowing because of the severe pain. He has a fever over 101°F and white spots coat the throat

What is the expected benefit of antibiotic treatment in this patient?

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)

Streptococcus pyogenes (% Resistance)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance</th>
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<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>Levofoxacin</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

How Common is Penicillin Allergy?

- 500 patients with medical record history of “penicillin allergy” skin tested with penicilloyl-polylysine (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)

“Penicillin Allergy” and VRE

- Retrospective study: association of VRE and prior Hx of “penicillin allergy”
- Penicillin allergy
  General population: 6%
  VRE patients: 24% (p<0.001)
- Allergy to other drugs
  General population: 7%
  VRE patients: 33.6% (p<0.001)
  (Reddy et al: 2013 Annual Meeting of the American College of Allergy Asthma, Immunology)

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?

Acute Bronchitis

- 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)
Acute Bronchitis

- 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

Resistance and Superinfection: the Influence of Antibacterials

Causal associations between antimicrobial use and the emergence of resistance

- Changes in antimicrobial use are paralleled by changes in the prevalence of resistance
- Resistance is more common in health care-associated bacterial infections compared with community-acquired
- When compared with controls, patients harboring resistant organisms are more likely to have received prior antimicrobials
- Areas within hospitals (i.e. critical care units) that have the greatest rate of antimicrobial resistance also have the greatest rate of antimicrobial use
- Increasing the duration of patient exposure to antimicrobials increases the likelihood of colonization with resistant organisms
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)

### 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>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>


### Risk Factors for Multidrug-Resistant *P. aeruginosa*

- Immunocompromised state
- Length of hospital stay
- Mechanical ventilation
- Prolonged antimicrobial use**

(Pharmacotherapy 2005; 25: 1353)
Barriers to Appropriate Antimicrobial Use

- Prescribers do not believe that their prescribing patterns are linked to resistance, toxicity, inefficient cost
- Patients do not believe that their demands for antibiotics are linked to resistance.
- Linking changes in antimicrobial use with nosocomial resistance patterns is logistically difficult: infection control problems, outpatient antibiotic usage, multiple confounders

Barriers to Appropriate Antimicrobial Use

- Physicians are not consistently reimbursed for oversight of programs associated with the appropriate use of antimicrobials
- Budgetary maintenance can be a disincentive for pharmacy involvement toward the improved use of antimicrobials

CDC 12-Step Program to Prevent Antimicrobial Resistance

**Prevent Infection**
1. Vaccinate
2. Remove catheters

**Diagnose and Treat Infection Effectively**
3. Target the likely pathogen
4. Access the experts

**Use Antimicrobials Wisely**
5. Practice antimicrobial control
6. Use local data
7. Treat infection, not contamination
8. Treat infection, not colonization
9. Know when to say “no” to vancomycin
10. Stop treatment when infection is cured or unlikely
Antibacterial-resistant *Staphylococcus aureus* is Associated with Increased Cost and LOS

- Surgical site infection: MRSA associated with increase in LOS of 5 days after infection. Charges were $29,455 for controls, $52,791 for MSSA, $92,363 for MRSA (Clin Infect Dis 2003; 36: 592)
- Bacteremia: MRSA bacteremia associated with a median attributable length of stay of 2 days and a median attributable increase in hospital charge of $6,916 (Infect Control Hosp Epidemiol 2006; 26: 166)
- Ventilator-associated pneumonia: MRSA associated with increase in 5.3 ICU days, 3.8 days LOS, 4.4 days receiving mechanical ventilation, when compared to MSSA (Crit Care 2006; 10: 157)

Antibacterial-resistant Gram Negative Infection is Associated with Increased Cost and LOS

- Fluoroquinolone-resistant *P. aeruginosa*: Patients infected with fluoroquinolone-resistant gram negative *P. aeruginosa* had greater median hospital charges when compared with FQ-susceptible *P. aeruginosa* ($62,325 vs $48,734) (Am J Med 2006; 119: 527.e19-25)
- Surgical patients with postoperative infection: Infection with resistant GNR associated with an incremental cost of $11,075 (Crit Care Med 2007; 35: 89)

Superinfection is Associated with Increased Cost and LOS

- *Clostridium difficile*-associated diarrhea (CDAD) in the critical care unit is associated with increased LOS, i.e. 6.1 D vs 3.0 D, and increased ICU cost, i.e. $11,353 vs $6,028 (Infect Control Hosp Epidemiol 2007; 28: 123)

CDC 12-Step Program to Prevent Antimicrobial Resistance

*Prevent Transmission*

11. Isolate the pathogen
12. Break the chain of contagion
Medicare Payment

- As of October 2008, in the United States, Medicare does not pay for conditions that result from preventable errors.
- “The hospital cannot bill the beneficiary for any charges associated with the hospital-acquired complication.”
- Private insurers are also adopting these mandates.

Non-reimbursable Conditions

1. Catheter-associated urinary tract infection
2. Catheter-associated vascular infections
3. Pressure ulcers
4. Objects left during surgery
5. Air embolism
6. Blood incompatibility
7. Mediastinitis
8. Falls

Non-reimbursable Conditions (yet to be confirmed)

1. *Staphylococcus aureus* bacteremia
2. Ventilator-associated pneumonia
3. *Clostridium difficile*-associated diarrhea

Outpatient Interventions Intended to Reduce Antimicrobial Resistance Selection Pressure
Antimicrobial Use in Acute Bronchitis

- 2462 adult patients at baseline and 2027 patients in intervention study
- Full intervention: household and office-based patient educational materials and clinician education, practice-profiling, academic detailing
- Limited intervention: office-based educational materials

(JAMA 1999; 281: 1512)

Antimicrobial Use in Acute Bronchitis

- Full intervention site: decline in antibiotic prescription rates from 74% to 48%
- Limited intervention site: 82% to 77%
- Control: 78% to 76%
- No difference in nonantibiotic prescriptions (bronchodilators, cough suppressants, analgesics) and return office visits between groups

(JAMA 1999; 281: 1512)

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)


“The desire to ingest medicines is one of the principle features which distinguish man from the animals.”

Sir William Osler

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)*

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)*

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)*

Proportion of patients developing IBD and antianaerobic antibacterial status

*P<0.001*

*(Pediatrics 2012; 130: e794)*
Triclosan: In Your Soap?

Many, many liquid and bar soaps contain an additional antibacterial agent, i.e. triclosan

What is the benefit?
Products Containing Triclosan

- **Soap**
- **Dental Care**: Colgate Total®
- **Cosmetics**: Garden Botanika® Powder Foundation; Mavala Lip Base; Paul Mitchell Detangler Comb, Bath and Body Works Antibacterial Moisturizing Lotions etc
- **Deodorant**: Arm and Hammer® Essentials Natural Deodorant and others

(\url{http://www.beyondpesticides.org/antibacterial/products.php})

Triclosan Efficacy

- Proven to be effective in the prevention of hospital-acquired infection, but less so than other agents
- Also effective in the prevention of plaque and periodontitis in adults with previous disease
- No current data confirms extra health benefits from having antibacterial-containing cleansers in homes
- American Medical Association: “Despite their recent proliferation in consumer products, the use of antimicrobial products, such as triclosan in consumer products has not been studied extensively. No data support their efficacy when used in products or any need for them…it may be prudent to avoid the use of antimicrobial products in consumer products.”
Triclosan and Resistance

- No convincing evidence to support the contention that triclosan usage has resulted in the development of resistant bacteria…however, many examples of induced resistance (mycobacteria, Salmonella, Pseudomonas) in the laboratory setting, including reduced susceptibility of quinolones, tetracyclines, ampicillin.

Triclosan: other effects

- Animal studies have shown interference with hormones critical for normal development and function of the brain and reproductive system. Triclosan has been associated with lower levels of thyroid hormone and testosterone. Another agent, triclocarban has been shown to artificially amplify the effects of sex hormones such as estrogen and testosterone.

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 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