Evidence-Based Management of Acute Respiratory Tract Infections

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OUTLINE

Focus on “evidence updates”

- Unintended Consequences of Antibiotic Use
- Acute Sinusitis
- Acute Pharyngitis
- Acute Bronchitis
Antibiotic Use

- Development of New Resistant Clones
- Transmission of Existing Resistant Clones

Antimicrobial Resistance

Adverse Effects of Antibiotic Treatment

- Allergic Reactions
- Nausea/Cramps/Diarrhea
- Yeast Infections
  - 6/27 (Abx+) vs. 0/27 (control)... About 20-25% risk
  - 55/235 (23% (95% CI: 18% to 29%)) women developed post-antibiotic vulvovaginitis. Compared with placebo, the odds ratio with oral lactobacillus was 1.06 (95% CI: 0.58 to 1.94) and with vaginal lactobacillus 1.38 (0.75 to 2.54).
    - BMJ. 2004 Sep 4;329(7465):548.
- Promote Clostridium difficile
- Unnecessary costs
- Medicalization of illness
Antibiotic-Associated Diarrhea

- Meta-analysis of 63 RCTs, which included 11,811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD
  - relative risk, 0.58; 95% CI, 0.50 to 0.68; P < .001
  - number needed to treat, 13; 95% CI, 10.3 to 19.1
  - Majority used Lactobacillus-based treatment alone or in combination with other genera.

JAMA. 2012 May 9;307(18):1959-69

Fluoroquinolone Side Effects

- Tendon Rupture: 3x Risk
  - The 90-day risk of Achilles tendon ruptures among FQ users was 17.7/100,000 (95% CI: 5.7-41.3) vs. 5.7/1000,000 baseline.

- Retinal Detachment
  - Increase risk = 4 per 10,000 person-years
  - NNH = 2500 any FQ users
Azithromycin and Cardiovascular Health


Abx Resistance Reversal is Possible!

Table: Time Trend in S. pneumoniae resistance following single mass Azithromycin treatment in Ethiopia for trachoma prevention

<table>
<thead>
<tr>
<th>Group and time of sampling</th>
<th>S. pneumoniae carriage, no. of subjects (% [95% CI])</th>
<th>Resistance level, % of isolates [95% CI] by agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Tetacycline</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months (n = 120)</td>
<td>111 (92.5 [89.2–96.7])</td>
<td>28.2 (18.4–38.6)</td>
</tr>
<tr>
<td>36 months (n = 120)</td>
<td>104 (95.7 [92.5–99.9])</td>
<td>26.3 (16.3–36.1)</td>
</tr>
<tr>
<td>42 months (n = 120)</td>
<td>111 (92.8 [90.0–96.7])</td>
<td>30.6 (19.9–40.4)</td>
</tr>
<tr>
<td>54 months (n = 120)</td>
<td>112 (93.3 [89.2–98.3])</td>
<td>20.8 (12.7–30.7)</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months (n = 120)</td>
<td>112 (93.3 [90.9–97.5])</td>
<td>0.9 (0.9–3.5)</td>
</tr>
<tr>
<td>36 months (n = 119)</td>
<td>113 (95.0 [88.7–100.0])</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

* Prevalence estimates represent the no. of resistant isolates per no. of total isolates. All measurements are means of 8 state team clusters shown with bootstrapped 95% CIs (10,000 replications). CI, confidence interval; TMP-SMX, trimethoprim-sulfamethoxazole.

** The last azithromycin treatment was administered to the treated group at 30 months.

## Potential Reductions Abx Rx for ARIs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Visits</th>
<th>Rx Rate</th>
<th>Bact %</th>
<th>Abx Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otitis Media</td>
<td>13 x 10^6</td>
<td>76%</td>
<td>65%</td>
<td>1.1 million</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11 x 10^6</td>
<td>70%</td>
<td>40%</td>
<td>3.5 million</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>14 x 10^6</td>
<td>62%</td>
<td>25%</td>
<td>5.2 million</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>13 x 10^6</td>
<td>59%</td>
<td>10%</td>
<td>6.5 million</td>
</tr>
<tr>
<td>URI/cold</td>
<td>25 x 10^6</td>
<td>30%</td>
<td>5%</td>
<td>6.2 million</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>76 x 10^6</td>
<td>54%</td>
<td>25%</td>
<td>22.5 million</td>
</tr>
</tbody>
</table>

Data source: NAMCS, 1998

## Communicating with Patients
-how to help patients say “no” to Abx for viral ARIs

- Illness labeling: use “chest cold”, not “bronchitis”
- Validate illness severity; focus on symptom relief
- Provide a contingency plan
- Discuss downside of unnecessary antibiotic use
  - risk of carriage/spread of antibiotic-resistant bacteria
- Patient-physician communication
  - Explain the illness
  - Spend “enough” time
  - Treat with respect
MANAGEMENT OF ACUTE RHINOSINUSITIS

Most cases of rhinosinusitis are viral

- Viral URI: X-ray shows 39% sinus involvement, and CT shows 87% sinus involvement.
“The clinical diagnosis of acute bacterial rhinosinusitis should be reserved for...” [B]

1. Rhinosinusitis symptoms ≥ 7 days
2. Purulent nasal secretions
3. Maxillary pain/tenderness in face/teeth

“...rarely some patients with acute bacterial rhinosinusitis present with dramatic symptoms of severe unilateral maxillary pain, swelling and fever”
2004 Consensus Conference
AAAAI, AAOA, AAOHNS, ACAAI, ARS

- Viral for first 10-14 days unless complicating features
  - Severe headache or facial pain
  - High fever
  - Impending/actual complications to eye, lung, brain
    - Local redness and edema
    -Visual disturbances
    - Delerium


How Good Are These Criteria?

- Cx (+) sinus aspirate
- Purulent sinus aspirate
- CT scan
- Xray
- High clinical suspicion
- Sinus symptoms

(a) CT scan criteria of air-fluid level or complete opacification.
(b) Xray criteria of mucosal thickening, air-fluid level or complete opacification.
Garbutt RCT, 2012. CDC Criteria

<table>
<thead>
<tr>
<th>Treatment Outcomes</th>
<th>Amoxicillin (n=85)</th>
<th>Control (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in SNOT-16 scores from day 0, mean (95% CI)²</td>
<td>0.59 (0.47-0.71)</td>
<td>0.54 (0.41-0.67)</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.06 (0.90-1.23)</td>
<td>0.96 (0.71-1.20)</td>
</tr>
<tr>
<td>Day 10</td>
<td>1.23 (1.06-1.37)</td>
<td>1.20 (1.07-1.32)</td>
</tr>
</tbody>
</table>

Self-reported significant improvement

<table>
<thead>
<tr>
<th>In symptoms since day 0, % (95% CI)</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 (27-48)</td>
<td>34 (23-45)</td>
<td>29 (21-38)</td>
<td>.67</td>
</tr>
<tr>
<td>74 (64-83)</td>
<td>56 (45-67)</td>
<td>61 (52-71)</td>
<td>.02</td>
</tr>
<tr>
<td>78 (69-87)</td>
<td>80 (71-90)</td>
<td>81 (72-91)</td>
<td>.71</td>
</tr>
</tbody>
</table>

| Period missed from work, mean (95% CI), d | 0.55 (0.28-0.82) | 0.55 (0.22-0.87) | .99 |

| Period unable to do usual network activities, mean (95% CI), d | 1.15 (0.76-1.54) | 1.67 (1.08-2.26) | .14 |

| Relapse rate, % (95% CI) | 9 (3-16) | 6 (1-11) | .57 |
| Recurrence rate, % (95% CI) | 6 (1-11) | 2 (0-6) | .44 |
| Satisfaction with treatment, % (95% CI) | 53 (42-64) | 41 (29-52) | .13 |

IDSA Guidelines, 2012

- Diagnosis of ABRS. Signs and symptoms...
  - Persistent and not improving ≥ 10 days
    OR
  - Severe (≥ 3-4 days) (e.g. fever + facial pain + purulence)
    OR
  - Worsening/”double-sickening” (≥ 3-4 days) after initial URI
### IDSA Guidelines, 2012

**Antibiotic Rx based on Risk of Resistance**
- Age <2 or >65 years, daycare
- Prior antibiotics within 30 days
- Prior hospitalization past 5 days
- Comorbidites
- Immunocompromised

**Duration of Rx**
- Improvement after 3-5 days
  - Complete 5-7 days if low risk resistance/first-line therapy
  - Complete 7-10 days if high risk resistance/second-line therapy
- Worsening/no improvement after 3-5 days... broaden/switch
  - Improvement... complete 5-7 or 7-10 days
  - Worsening or no improvement after 3-5 days... Refer to specialist

### Antibiotic Treatment for Sinusitis

**First Line (ACP)**
- Amoxicillin, 1.5 to 3.5 g/d divided 2-3 times daily
- Trimethoprim-sulfa (800/160 mg twice daily)**

**Second Line (ACP)**
- Amoxicillin-clavulanate (500/125 mg 3 times daily)*
- 2nd or 3rd generation cephalosporins
- Doxycycline, 200 mg day 1, then 100 mg twice daily*
- Macrolides (clarithromycin or azithromycin)**

*IDSA recommends amoxicillin-clavulanate as first-line, and doxycycline as the first-choice alternative.

**IDSA does not recommend these as empiric Rx for ABRS
Complications of acute bacterial rhinosinusitis

• Sinus cavernous thrombosis
  ○ Fever; Headache; Diplopia/Visual Disturbances

• Orbital cellulitis
  ○ Fever; Headache/eye pain; orbital or periorbital cellulitis

• Intracranial extension (meningitis; brain abscess)
  ○ Fever; delerium; meningismus

Rhinosinusitis Summary (2)

• The key clinical question in evaluating adolescents and adults with acute rhinosinusitis is whether they are likely to benefit from antibiotic therapy.
  ○ In patients with clinical features of bacterial rhinosinusitis, reserve antibiotic treatment for those with moderate to severe symptoms
  ○ Patients with fever and severe symptoms, consider immediate treatment and referral to ENT for possible drainage.

• Improving sinus drainage and congestion can be achieved with a number of medications, including nasal corticosteroids, nasal and oral decongestants, and saline lavage.
**MANAGEMENT OF ACUTE PHARYNGITIS**

- Gram negative anaerobe.
- Causative agent in Lemierre syndrome (septic thrombophlebitis)
- In 15-30 yo, causes about 10% of cases (similar to GAS)
- **Not responsive to macrolides**
- Suspect in adolescent/young adult with worsening Sx and neck swelling
More relevant than group A strep?

### Table: Hypothetical Cohort of 1 Million Patients Aged 15 to 24 Years With Pharyngitis

<table>
<thead>
<tr>
<th>Outcomes, by Type of Pharyngitis</th>
<th>Events per 1,000,000 Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A streptococcus</strong></td>
<td>100,000</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>50†</td>
</tr>
<tr>
<td>Complex acute rheumatic fever</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fusobacterium necrophorum</strong></td>
<td>100,000</td>
</tr>
<tr>
<td>The Leniere syndrome</td>
<td>250†</td>
</tr>
<tr>
<td>Long-term disability (11)</td>
<td>20†</td>
</tr>
<tr>
<td>Death</td>
<td>115</td>
</tr>
</tbody>
</table>

Clinical Epidemiology GAS

CDC Principle 1.0

**ADULTS**
- GAS is the causal agent in about 10% of adult cases

**CHILDREN**
- GAS is the causal agent in about 30% of pediatric cases
- Approximately 10% are colonized with GAS

**CLINICAL FEATURES**
- GAS: fever, tonsillar exudates, tender lymphadenopathy
- Viral: conjunctivitis, coryza, cough
### ADULT Pharyngitis

**Principle 4.0. Role of Cultures**

- “Throat cultures are not recommended for routine primary evaluation of adults with pharyngitis or for confirmation of negative results on rapid antigen tests when rapid test sensitivity exceeds 80%.” [A]

### Pediatric Pharyngitis

**CDC Principles. Clinical Screen**

- Score 0-1: no test, no treatment
- No test, empiric treatment
  - Scarlet Fever
  - GAS + household contact and pharyngitis
- Culture confirmation of negative RADT
  - When sensitivity of RADT < 90%
**Adult and Pediatric Pharyngitis**

**CDC Principle 5.0. Antibiotic Choice**

- Amoxicillin qd or bid x 10 days (or PCN VK)
  - Cephalosporin as alternative to PCN-allergic
  - Macrolides as second-line treatment
    - *Does not cover Fusobacterium spp.*

- IM Benzathine penicillin

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**Complications of acute pharyngitis**

- Peritonsillar abscess
  - Fever, trismus, uvula deviation

- Rheumatic fever
  - Fever, rash, arthralgias, carditis

- Epiglotitis
  - Fever, rapid evolution, difficulty with secretions, benign oropharynx

- Otitis Media and Sinusitis (children)
  - Cochrane shows reduction 50% with abx treatment
Acute Pharyngitis Summary

- GAS pharyngitis is more likely when patients present with history of fever, absence of cough, tonsillar exudates, and tender cervical lymphadenopathy
  - Consider Fusobacterium in young adults
- Symptomatic benefits of antibiotic treatment of GAS require treatment 48-72 hours

MANAGEMENT OF ACUTE COUGH ILLNESS AND ACUTE BRONCHITIS
Acute Bronchitis
- Definition (in guidelines)

- Acute or subacute (< 3 weeks) cough illness in adolescents or adults without underlying lung disease
  - DDx includes pneumonia, pneumonitis, asthma, CHF, esophagitis...

- To distinguish from other ARIs (cold, sinusitis, pharyngitis), cough should be the prominent symptom

Acute Bronchitis
- Potential etiologies

- **Bacterial**
  - M. pneumoniae
  - C. pneumoniae
  - B. pertussis

- **Viral**
  - influenza
  - Parainfluenza
  - RSV
  - rhinovirus
  - coronavirus
  - adenovirus
  - metapneumovirus

- **Unknown**
Acute Bronchitis
-pathophysiology

- Acute Phase (1-5 days)
  - inflammatory cell activation; cytokine release
  - constitutional symptoms (fever, malaise)
- Protracted Phase (1-3 weeks)
  - bronchial hypersensitivity
    - vagal; adrenergic tone; IgE-mediated histamine release
  - cough ± phlegm; wheezing
  - agent independent

Acute Bronchitis
-bronchial hyperresponsiveness

Airflow obstruction in acute bronchitis without underlying lung disease

Eur Resp J 1994;7:1239
**Pertussis**
...not just for children anymore

- DPT-related immunity wanes as early as 3 years... and absent after 10-12 years
- attack rates as high as 100%
- 10-15% adults seeking care for persistent cough (>3 wks) have evidence of pertussis
- No clinical features distinguish pertussis in previously immunized adults (Cornia PB et al, JAMA 2010)

**Pertussis**

- **Diagnosis**
  - Dacron nasopharyngeal swab or nasal saline wash
  - PCR is now standard...
    - No FDA-licensed tests yet...
  - Coordinate with public health dept
- **Treatment**
  - Macrolides; trimethoprim-sulfa
  - Probably won’t help cough duration if started after 10 days of illness
  - Reasonable to provide empirical Abx treatment to contacts with cough, and close contacts/household members as prophylaxis.
PREVENTION: Pertussis Boosters
- ACIP/CDC Recommendations

• Routine
  ○ Single Tdap instead of dT at age 11-18
  ○ Tdap (instead of dT) in adults 18-64 if > 10 years since dT

• Tdap when dT within 2-10 years
  ○ Adult contacts of infants < 12 months
    • Women prior to pregnancy; else post-partum
  ○ Healthcare workers (all staff)
  ○ Rare Adverse Events
    • Arthus Reaction
    • Extensive Limb Swelling

Clinical Algorithm for Adults with Acute Cough Illness

Low Prob Pneumonia: nl vital signs + nl lung exam
• no chest xray
• no antibiotic Rx

Interm Prob Pneumonia: abnl vital signs OR abnl lung exam
• consider chest xray

High Prob Pneumonia: abnl vital signs + abnl lung exam
• chest xray
• consider empiric antibiotic Rx
Uncomplicated Acute Bronchitis
- azithromycin vs. vitamin C (Lancet 2002;359;1648-54)

Return to Usual Activities

OTC Cough Therapies
-Cochrane Reviews

- **Antitussives**
  - codeine: 2 trials; no differences
  - dextromethorphan: 2 of 3 trials show benefit
- **Expectorants (guaifenesin):** 1 of 2 trials benefit
- **Mucolytics:** 1 trial inconsistent benefit
- **Antihistamine-Decongestant Combinations**
  - 1 of 2 trials show benefit
- **Dextro-salbutamol:** reduced nocturnal cough only
Acute cough illness treatment
-bronchodilator treatment

Randomized, placebo controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Patients</th>
<th>Treatment</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melbye</td>
<td>bronchitis</td>
<td>73</td>
<td>fenoterol aerosol</td>
<td>Decrease symptoms</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td></td>
<td></td>
<td>Improved FEV1</td>
</tr>
<tr>
<td>Hueston</td>
<td>bronchitis</td>
<td>34</td>
<td>oral albuterol vs.</td>
<td>Decrease cough @ 1 week</td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td></td>
<td>erythromycin</td>
<td>(41% vs. 82%)</td>
</tr>
<tr>
<td>Hueston</td>
<td>bronchitis</td>
<td>46</td>
<td>albuterol aerosol vs.</td>
<td>Decrease cough @ 1 week</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td>(placebo + erythro)</td>
<td>(61% vs. 91%)</td>
</tr>
<tr>
<td>Littenberg</td>
<td>nonspecific</td>
<td>104</td>
<td>albuterol aerosol</td>
<td>No benefit</td>
</tr>
<tr>
<td>1996</td>
<td>cough</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What’s the Difference Between a Chest Cold and Bronchitis?

"How often are antibiotics necessary to get better?"

*%p=0.001

- chest cold
- bronchitis
- chest cold = bronchitis

(chest cold and bronchitis different (n=269)
(chest cold = bronchitis (n=76)
Acute Bronchitis Summary (1)

- Acute bronchitis represents an ARI in adolescents and adults < 3 weeks duration, in which cough is the prominent symptom, and in which clinical criteria for pneumonia or sinusitis are absent.
- The etiology is viral in the vast majority of cases.
- Pneumonia is unlikely when vital signs & chest exam normal
  - Intermediate probability pneumonia exists when at least 1 vital sign or chest examination is abnormal.
  - High probability of pneumonia exists when both vital signs and chest examination is abnormal.
  - Pneumonia presents atypically in the elderly and immunosuppressed.

Acute Bronchitis Summary (2)

- Nine RCTs of antibiotic treatment of uncomplicated acute bronchitis in adolescents and adults show no significant clinical benefit.

- The most effective treatments for reducing cough duration and/or severity include dextromethorphan, codeine, and albuterol.

- If community-acquired pneumonia is suspected antibiotic treatment with amoxicillin or doxycycline is indicated.