Death, Taxes, and Antibiotic Resistance: The Certainties of Life

Bradley L. Smith, Pharm.D.

Pharmacy Grand Rounds
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History of Antibiotics

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body…Moral: if you use penicillin, use enough”

Fleming, A. Nobel Lecture, 11 Dec 1945
Presentation Objectives

• Identify mechanisms of antibiotic resistance
• List methods to combat antibiotic resistance
• Describe arguments for appropriate duration of antibiotic therapy
Antibiotic Resistance

Antibiotic Resistance

- **Transformation**
  - *Haemophilus* spp
  - *Streptococcus* spp
  - *Neisseria* spp

- **Transduction**
  - *E. coli*
  - *Pseudomonas* spp
  - *Salmonella* spp
  - *Staphylococcus* spp

- **Conjugation**
  - *E. coli*
  - *Mycobacterium* spp

Furuya, EY et al. *Nat Rev Microbiol.* 2006; 4: 36-45
Mechanisms of Antibiotic Resistance

- Enzymatic alterations

- Enzymatic destruction

Munita, JM et al. Microbiol Spectr. 2016; 4(2)
Mechanisms of Antibiotic Resistance

Decreased cellular entry

Production of efflux pumps

Munita, JM et al. Microbiol Spectr. 2016; 4(2)
Mechanisms of Antibiotic Resistance

- Target site mutation
- Replace/bypass target site

Munita, JM et al. *Microbiol Spectr.* 2016; 4(2)
What do transduction, transformation, and conjugation have in common?

a) All require presence of an outside factor to facilitate gene transfer
b) In all three processes, DNA is transferred as a single stranded molecule
c) They all transfer large pieces of DNA into recipient cells
d) All of the above
e) None of the above
Causes of Antibiotic Resistance

1. Overuse of Antibiotics
2. Misuse of Antibiotics
3. Slowed Antibiotic Pipeline
4. Agricultural Use

Overuse of Antibiotics

“Public will demand [the drug and]…then will begin an era …of abuses”

– A. Fleming

CDC Website. 2014.
Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010 – 2011

- 184,032 visits surveyed
- 506 prescriptions written per 1000 population
- Most frequent conditions were sinusitis, otitis media, and pharyngitis
- 353 prescriptions per 1000 population estimated appropriate (69.8%)

Antibiotic Resistance Management Strategies

- Antibiotic Stewardship Programs
- Government Legislation
- Improve Prescribing Practices
- Prevent Transmission
- Improve Diagnosis

Antibiotic Stewardship Programs

- Program at Mayo Clinic:
  - Antibiotic Stewardship
  - Restricted formulary
  - Mayo Clinic Antimicrobial Therapy Quick Guide
  - Infection Control Policies
  - Local antibiogram
Improve Prescribing Practices

- “Delayed prescription”
- Education campaigns for patients

Antibiotics Aren’t Always the Answer

Antibiotics only treat bacterial infections. Viral illnesses cannot be treated with antibiotics. When an antibiotic is not prescribed, ask your healthcare professional for tips on how to relieve symptoms and feel better.

<table>
<thead>
<tr>
<th>Illness</th>
<th>Usual Cause</th>
<th>Antibiotic Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold/Runny Nose</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Bronchitis/Chest Cold (in otherwise healthy children and adults)</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Whooping Cough</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Flu</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Strep Throat</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Sore Throat (except strep)</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Fluid in the Middle Ear (otitis media with effusion)</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

www.cdc.gov/getsma
# Prescription Strategies in Acute Uncomplicated Respiratory Infections

<table>
<thead>
<tr>
<th>Design</th>
<th>Open-Label, randomized trial (n = 405)</th>
</tr>
</thead>
</table>
| **Population**          | • Adults with acute pharyngitis, rhinosinusitis, acute bronchitis, or exacerbation of mild-to-moderate COPD  
                          • Reasonable doubt for antibiotic treatment |
| **Exclusion**           | • Previous participation  
                          • Risk for serious complications due to previous comorbidity |
| **Intervention**        | • No prescription  
                          • Immediate prescription  
                          • Prescription collection  
                          • Patient-led prescription |
Prescription Strategies in Acute Uncomplicated Respiratory Infections

- Demographics
  - Middle-aged women
  - Non-smokers

- Common Symptoms
  - Cough
  - Difficulty sleeping

<table>
<thead>
<tr>
<th></th>
<th>Immediate Mean (SD)</th>
<th>Collection Mean (SD)</th>
<th>Patient-led Mean (SD)</th>
<th>No Prescription Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
</table>
| Maximum Severity of any symptom^a  
  [Median (IQR)]                | 5 (3-5)             | 5 (3-5)              | 5 (4-5)               | 5 (4-6)                   | 0.009   |
| Duration of Severe Symptoms  
  [Mean (SD)]                    | 3.6 (3.3)           | 4.0 (4.2)            | 5.1 (6.3)             | 4.7 (3.6)                 | 0.002   |

Delayed strategies were associated with slightly greater but clinically similar symptom burden and duration compared with an immediate strategy.

^aBased on Likert Scale from 0 (no problem) to 6 (as bad as it could be)  
Improve Diagnosis

• Shortens empiric therapy

• Rapid diagnostic tests allow for quicker, more definitive identification
  • Influenza
  • Respiratory syncytial virus
  • Strep throat
  • mecA gene
  • Methicillin-resistant *S. aureus* nares swab
  • Gastrointestinal viral panel
  • Respiratory viral panel
Prevent Transmission

• Mayo Clinic infection control programs
  • Annual required training
  • Isolation precautions
  • Hand hygiene

• Vaccinations
  • Influenza
  • Pneumococcal
The most effective method of preventing the transmission of antibiotic resistant organisms is

a) “Delayed prescription”

b) Hand washing

c) Using rapid diagnostic tests

d) Using new antibiotic agents
Are shorter courses of antibiotics sufficient to effectively treat common bacterial infections?
Antibiotic Therapy Duration

Factors to consider:
- Treatment end point
- Agent chosen
- Factors to consider
- Ability for source control
- Virulence of the organism
- Host immune system

Llewelyn, MJ et al. BMJ. 2017. 358: j3418
### Design
Randomized, double-blind, placebo-controlled, non-inferiority trial (n = 119)

### Population
- Non-pregnant adults with clinical signs of pneumonia
- Body temperature >38°C
- Radiological evidence of new infiltrate
- Pneumonia severity index ≤ 110

### Exclusion
- History of amoxicillin allergy
- Immunocompromised
- Antimicrobial treatment for >24 hours prior
- Concomitant infection requiring antibiotics
- Admittance to intensive care unit
- Suspicion of aspiration, atypical, *Klebsiella*, or staphylococcal pneumonia

### Intervention
- Amoxicillin 1000mg IV q6h x3d
  - Amoxicillin 750mg PO TID x5d
  - Oral placebo TID x5d

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el Moussaoui, R et al. *BMJ.* 2006. 332: 1355 – 60

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Discontinuing Antibiotic Treatment After 3 Days vs 8 Days in Mild to Moderate-Severe Community Acquired Pneumonia

- Demographics
  - Middle-aged men
  - Non-smokers

- Common pathogens
  - *S. pneumoniae*
  - *H. influenzae*

<table>
<thead>
<tr>
<th></th>
<th>3 days of therapy</th>
<th>8 days of therapy</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success at day 10 [n(%)]</td>
<td>50 (93)</td>
<td>56 (93)</td>
<td>-9 to 10</td>
</tr>
<tr>
<td>Clinical success at Day 28 [n(%)]</td>
<td>47 (90)</td>
<td>49 (88)</td>
<td>-9 to 15</td>
</tr>
<tr>
<td>Mean hospital length of stay (days)</td>
<td>7.9</td>
<td>8.9</td>
<td>-1.3 to 3.2</td>
</tr>
</tbody>
</table>

Discontinuation of amoxicillin after 3 days in not inferior to discontinuation after 8 days in adults admitted to the hospital with mild to moderate-severe community acquired pneumonia who show substantial improvement.

# Ciprofloxacin for 7 Days Versus 14 Days in Women With Acute Pyelonephritis

<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, double-blind, placebo-controlled, non-inferiority trial (n = 248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults with at least one sign or symptom of pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>Fever ≥ 38°C</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Pregnancy or lactation</td>
</tr>
<tr>
<td></td>
<td>Known fluoroquinolone hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Antibiotic treatment in previous 72 hours</td>
</tr>
<tr>
<td></td>
<td>Indwelling catheter or intermittent catheterization</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance &lt;30 mL/min</td>
</tr>
<tr>
<td></td>
<td>Convulsive disease</td>
</tr>
<tr>
<td>Intervention</td>
<td>Ciprofloxacin 500mg BID x7d + placebo BID 7d</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 500mg BID x14d</td>
</tr>
</tbody>
</table>

Ciprofloxacin for 7 Days Versus 14 Days in Women With Acute Pyelonephritis

- **Demographics**
  - Middle-aged
  - Healthy

- **Common pathogens**
  - *E. Coli*
  - *S. saprophyticus*

<table>
<thead>
<tr>
<th></th>
<th>7 days of therapy</th>
<th>14 days of therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term efficacy</td>
<td>71 (97)</td>
<td>80 (96)</td>
<td>0.004</td>
</tr>
<tr>
<td>[n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term efficacy</td>
<td>68 (93)</td>
<td>78 (93)</td>
<td>0.015</td>
</tr>
<tr>
<td>[n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment of acute pyelonephritis with 7 days of ciprofloxacin is non-inferior to 14 days of treatment

### Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, double-blind, placebo-controlled, non-inferiority trial (n = 520)</th>
</tr>
</thead>
</table>
| **Population** | 6 to 23 months of age  
Received at least 2 doses of pneumococcal conjugate vaccine  
Diagnosed acute otitis media  
Score of 3 or more on the AOM-SOS scale  
Presence of middle-ear effusion  
Moderate or marked bulging of tympanic membrane |
| **Exclusion** | Documented amoxicillin allergy  
Tympanic-membrane perforation  
Antimicrobial agent within previous 96 hours |
| **Intervention** | Amoxicillin/clavulanate 90mg/6.4mg per kilogram  
5 days treatment plus 5 days placebo  
10 days treatment |

AOM-SOS = Acute Otitis Media – Severity of Symptoms  
Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

- **Demographics**
  - 6 to 11 month males
  - Exposure to other children

- **Symptoms Severity**
  - AOM-SOS avg. = 8.4
  - Single ear affected

<table>
<thead>
<tr>
<th>Clinical failure – all children [n(%)]</th>
<th>10 days of therapy</th>
<th>5 days of therapy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 (16)</td>
<td>77 (34)</td>
<td>9 to 25</td>
<td></td>
</tr>
</tbody>
</table>

Number needed to treat to prevent clinical failure = 6

<table>
<thead>
<tr>
<th>Clinical failure rates by number of ears affected</th>
<th>10 days of therapy</th>
<th>5 days of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>One ear [n(%)]</td>
<td>10 (8)</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Both ears [n(%)]</td>
<td>29 (25)</td>
<td>51 (44)</td>
</tr>
</tbody>
</table>

p-value <0.001

Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

<table>
<thead>
<tr>
<th></th>
<th>10 days of therapy</th>
<th>5 days of therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom scores decreased by &gt;50%</td>
<td>211 (91)</td>
<td>181 (80)</td>
<td>0.003</td>
</tr>
<tr>
<td>[n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean monthly rate of recurrence</td>
<td>0.14±0.18</td>
<td>0.12±0.19</td>
<td>0.56</td>
</tr>
<tr>
<td>(episodes ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent culture revealed</td>
<td>85 (47)</td>
<td>78 (44)</td>
<td>0.58</td>
</tr>
<tr>
<td>colonization of penicillin resistant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pathogen [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reduced-duration treatment resulted in less favorable clinical success rates and did not lower the rate or resistance
Studies showed which of the following syndromes is best treated with >7 days of therapy

a) Community-acquired pneumonia

b) Pyelonephritis

c) Acute otitis media in children

d) All of the above
Next Steps

• Patient-centered vs duration-driven

• Continued research
  • “Patient feels better” approach
  • Resistance after treatment

• Continued patient and prescriber education
  • Treat vs not treat

• Continued stewardship
  • Inpatient and outpatient
Questions & Discussion

smith(bradley1@mayo.edu}