I HAVE NO DISCLOSURES OR CONFLICTS RELATED TO THIS LECTURE

Neil Fishman, MD
ANTIMICROBIAL MANAGEMENT: DESIGN, IMPLEMENTATION, AND EFFICACY

Neil Fishman, MD
University of Pennsylvania Health System
neil.fishman@uphs.upenn.edu
Evolution of Terminology

- Antibiotic Control
Evolution of Terminology

- Antibiotic Control
- Antimicrobial Management
Evolution of Terminology

- Antibiotic Control
- Antimicrobial Management
- Antimicrobial Stewardship
ANTIMICROBIAL STEWARDSHIP INTERVENTIONS: DESIGN, IMPLEMENTATION, AND EFFICACY
You can’t always get what you want...
<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 B.C.</td>
<td>“Here, eat this root.”</td>
</tr>
<tr>
<td>1000 A.D.</td>
<td>“That root is heathen. Here, say this prayer.”</td>
</tr>
<tr>
<td>1850 A.D.</td>
<td>“That prayer is superstition. Here, drink this potion.”</td>
</tr>
<tr>
<td>1940 A.D.</td>
<td>“That potion is snake oil. Here, take this penicillin; it’s a miracle drug.”</td>
</tr>
<tr>
<td>1985 A.D.</td>
<td>“Penicillin is worthless. Here, take this new antibiotic; it’s bigger and better.”</td>
</tr>
<tr>
<td>2013 A.D.</td>
<td>“Those antibiotics don’t work any more. Here eat this root.”</td>
</tr>
</tbody>
</table>
Antimicrobial Stewardship: Design, Implementation and Efficacy

- Background
- Conceptual framework for use of antibiotics
- Strategies to improve antibiotic use
- HUP Antimicrobial Stewardship Program
  - Evaluation
- Impact analysis
  - Microbial ecology
  - CRE
Efforts to Control Resistance

- Antimicrobial Stewardship
- Develop New Drugs and Vaccines
- Improved Diagnostics
- Infection Control
- Research
- Education
- Public Policy
Efforts to Control Resistance

- Antimicrobial Stewardship
- Develop New Drugs and Vaccines
- Improved Diagnostics
- Infection Control
- Public Policy
- Research
- Education
Why Are We Having This Conversation?

- A lot of in-patient antibiotic prescriptions are unnecessary or sub-optimal.
- We are running out of antibiotics.
- We won’t get new ones anytime soon.
- Antimicrobial resistance is a significant clinical issue
- It is not just about resistance:
  - *C. difficile* infection
  - Increased toxicity and other adverse events
  - Increased morbidity and mortality
  - Increase length of stay
  - Increased cost of care
50% of antimicrobial use is either unnecessary or inappropriate

Reimann & D’Ambola. JAMA 1968;205:537
Unnecessary Use of Antimicrobials in Hospitalized Patients

- Prospective observational study in ICU
- 576 (30%) of 1941 antimicrobial days of therapy deemed unnecessary

Most Common Reasons for Unnecessary Days of Therapy

- Duration of Therapy Longer than Necessary: 192 days
- Noninfectious or Nonbacterial Syndrome: 187 days
- Treatment of Colonization or Contamination: 94 days

Why Does This Matter?

- 200-300 million antibiotics are prescribed annually
  - 45% for outpatient use
- 25-40% of hospitalized patients receive antibiotics
  - At least 30% are unnecessary or sub-optimal
  - 5% of hospitalized patients experience an adverse reaction
- >$1.1 billion spent annually on unnecessary adult antibiotic prescriptions for URI
  - 50-80% of outpatient antibiotic use is inappropriate
- **Antibiotics are unlike any other drug:** use of the agent in one patient can compromise efficacy in another
Outpatient antibiotic use: U.S.A. compared to Europe (2004)
Defined Daily Dose / 1,000 Inhabitants per day

United States: 24.9
Europe: 19.0
“Don’t forget to take a handful of our complimentary antibiotics on your way out.”
IS ANTIBIOTIC ABUSE A PROBLEM?

- Contributes to rising cost of medical care
- Increased adverse drug effects/reactions
  - 5% of hospitalized patients who receive antibiotics experience an adverse reaction
  - 20% of patients who require medical care have a history of an adverse drug effect
- Emergence of resistance
### Table 4. Distribution and Rank Order of Selected Pathogens Associate to the National Healthcare Safety Network, January 2006–October 2007,

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall*</th>
<th>CLABSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of pathogenic isolates</td>
<td>Rank</td>
</tr>
<tr>
<td>CoNS</td>
<td>5,178 (15.3)</td>
<td>1</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>4,913 (14.5)</td>
<td>2</td>
</tr>
<tr>
<td><em>Enterococcus species</em></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>1,177 (3.5)</td>
<td>3</td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>1,888 (5.6)</td>
<td>4</td>
</tr>
<tr>
<td>NOS</td>
<td>1,028 (3.0)</td>
<td>5</td>
</tr>
<tr>
<td><em>Candida species</em></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>2,295 (6.8)</td>
<td>6</td>
</tr>
<tr>
<td>Other <em>Candida spp.</em></td>
<td>1,333 (3.9)</td>
<td>7</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>3,264 (9.6)</td>
<td>8</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2,664 (7.9)</td>
<td>9</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1,956 (5.8)</td>
<td>10</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>1,624 (4.8)</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>902 (2.7)</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>359 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5,267 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33,848 (100)</td>
<td></td>
</tr>
</tbody>
</table>

**Note.** Of the 28,502 cases of HAI reported, 4,671 (16.4%) were polymicrobial associated bloodstream infection; CoNS, coagulase-negative staphylococci; NOS, no pneumonia.
# The Death of Antibiotics?

*Klebsiella pneumoniae*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>MIC interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>&gt;32</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>&gt;32</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>512</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;32</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;32</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32</td>
<td>I</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;10</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;10</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;2</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim/</td>
<td>&gt;4/80</td>
<td>R</td>
</tr>
<tr>
<td>sulfamethoxazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>&gt;8</td>
<td>R</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Fosfomycin*</td>
<td>26 mm</td>
<td>S</td>
</tr>
</tbody>
</table>
**Vital Signs: Carbapenem-Resistant Enterobacteriaceae**

**Abstract**

**Background:** Enterobacteriaceae are a family of bacteria that commonly cause infections in healthcare settings as well as in the community. Among Enterobacteriaceae, resistance to broad-spectrum carbapenem antibiotics has been uncommon. Over the past decade, however, carbapenem-resistant Enterobacteriaceae (CRE) have been recognized in healthcare settings as a cause of difficult-to-treat infections associated with high mortality.

**Methods:** The percentage of acute-care hospitals reporting at least one CRE from healthcare-associated infections (HAIs) in 2012 was estimated using data submitted to the National Healthcare Safety Network (NHSN) in 2012. The proportion of Enterobacteriaceae infections that were CRE was calculated using two surveillance systems: 1) the National Nosocomial Infection Surveillance system (NNIS) and NHSN (for 2001 and 2011, respectively) and 2) the Surveillance Network—USA (S3N) for 2010. Characteristics of CRE culture-positive episodes were determined using data collected as part of a population-based CRE surveillance project conducted by the Emerging Infections Program (EIP) in three states.

**Results:** In 2012, 4.6% of acute-care hospitals reported at least one CRE HAI (short-stay hospitals, 3.9%; long-term acute-care hospitals, 17.8%). The proportion of Enterobacteriaceae that were CRE increased from 1.2% in 2001 to 4.2% in 2011 in NNIS/NHSN and from 0% in 2001 to 1.4% in 2010 in TRN; most of the increase was observed in Klebsiella species (from 1.6% to 10.4% in NNIS/NHSN). In the EIP surveillance, 92% of CRE episodes occurred in patients with substantial healthcare exposures.

**Conclusions:** Carbapenem resistance among common Enterobacteriaceae has increased over the past decade; most CRE are associated with healthcare exposures.

**Implications for Public Health:** Interventions exist that could slow the dissemination of CRE. Health departments are well positioned to play a leading role in prevention efforts by assisting with surveillance, situational awareness, and coordinating prevention efforts.

**Introduction**

The Enterobacteriaceae are a large family of gram-negative bacilli that are normal inhabitants of the gastrointestinal tract of humans and other animals (1). These organisms are several decades have seen the spread of Enterobacteriaceae with resistance to broad-spectrum antibiotics; however, clinicians in the United States have relied on the carbapenem antibiotic class (imipenem, meropenem, doripenem,
ANTIBIOTICS
THE END OF MIRACLE DRUGS?

Warning: No longer effective against killer bugs.
REVENGE OF THE
Killer Microbes
Are we losing the
war against
infectious diseases?
Rating Children’s TV
What Parents REALLY Need to Know

“I Can’t Believe My Child Said That!”
Smart Comebacks for Embarrassed Moms and Dads

The Scary New Antibiotic Crisis

The Envelope, Please!
32 Terrific Toys
Our Annual Award Winners, Picked by Parents, Kids, and Other Experts

Finding the Perfect Baby Name...Again
BusinessWeek

SPECIAL REPORT  TELECOM's POWER PLAYERS  INVESTING  MUTUAL FUNDS: 1st QUARTER STARS

APRIL 6, 1998  A PUBLICATION OF THE McGRAW-HILL COMPANIES  $3.95

WAR AGAINST THE MICROBES
How drug makers are fighting back against a global resurgence of infectious disease.

PAGE 104

DR. DAVID SHLAES
OF WETZL & AVERST

Internet www.businessweek.com  America Online, Keyword: BW
### Impact of Antibiotic Resistance

<table>
<thead>
<tr>
<th>Organism</th>
<th>Increased risk of death (OR)</th>
<th>Attributable LOS (days)</th>
<th>Attributable cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA bacteremia</td>
<td>1.9</td>
<td>2.2</td>
<td>$6,916</td>
</tr>
<tr>
<td>MRSA surgical infection</td>
<td>3.4</td>
<td>2.6</td>
<td>$13,901</td>
</tr>
<tr>
<td>VRE infection</td>
<td>2.1</td>
<td>6.2</td>
<td>$12,766</td>
</tr>
<tr>
<td>Resistant Pseudomonas infection</td>
<td>3.0</td>
<td>5.7</td>
<td>$11,981</td>
</tr>
<tr>
<td>Resistant <em>Enterobacter</em> infection</td>
<td>5.0</td>
<td>9</td>
<td>$29,379</td>
</tr>
</tbody>
</table>

- Total cost of antimicrobial resistance is estimated to be **$30 billion annually**.

The Bottom Line

• Antimicrobial resistance is a critical patient safety issue
• Antimicrobial resistance is a public health threat
• Antibiotics should be viewed as a limited resource
• Antimicrobial stewardship provides the infrastructure to preserve antibiotics
Another Reason to Switch to Wegmans Pharmacy

Free antibiotics*

Stop by the Pharmacy today! Switching only takes a minute.

* Select generics only, with Shoppers Club Card and prescription. Antibiotics are not effective for viral infections, such as the common cold and the flu. See store or wegmans.com for list of items.
FREE Antibiotics

Up to a 14-day supply of the most commonly prescribed generic antibiotics with a valid prescription*

*With valid prescription. See pharmacist for details.
New Antibacterial Drugs Approved By FDA

Spellberg, CID 2004, Modified
The Pipeline is Dry

- Only 15-16 antibiotics are in development
- Only 8 of these have activity against key Gram negative bacteria
- None have activity against bacteria resistant to all current drugs

European Centre for Disease Prevention and Control/European Medicines Agency
Joint Technical Report
“The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy.”

-Dennis Maki, 1998
Antimicrobial Stewardship: Definition

• Processes designed to measure and optimize the appropriate use of antimicrobials

• Achieved by selecting the appropriate agent, dose, duration of therapy and route of administration
Antimicrobial Stewardship: Objectives

• Achieve optimal clinical outcomes
• Minimize toxicity and other adverse events
• Minimize development of antimicrobial resistance

May also reduce excessive costs attributable to:
• Inappropriate/unnecessary therapy
• Suboptimal outcomes
• Toxicity and other adverse events
• Antimicrobial resistance
Antimicrobial Stewardship Interventions

- Education
- Formulary restriction
- Prior approval
- Prospective Audit with Feedback (Streamlining)
- Cycling/rotation
- Computer-assisted programs
- Comprehensive programs
Knowledge of Infectious Diseases

Knowledge of Patient

Knowledge of Antibiotics

Decision to Use Antibiotics

Choice of Antibiotics

Physician’s Attitude

Availability of Antibiotics

Patient’s Attitude and Desires

Refine Choice of Antibiotics

Culture Results

CONCEPTUAL FRAMEWORK
Knowledge of Infectious Diseases

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CONCEPTUAL FRAMEWORK
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Antimicrobial Stewardship

Prior Approval
- Time consuming in real time
- Misses opportunities to de-escalate after antimicrobials started
- Less popular now because of concerns about inadequate empiric therapy and need for prompt antibiotic administration

Post-Prescription Review
- Time consuming but schedulable
- Uses prospective audit and feedback
- Harder to enforce unless there is the power to stop antibiotics
- Will not capture unnecessary or superfluous empiric therapy
Knowledge of Infectious Diseases

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PRIOR APPROVAL
PRIOR APPROVAL PROGRAMS

- Multiple approaches
  - Phone approval
  - Antibiotic order forms
  - Automatic stop orders
  - Direct interaction
  - Control categories
  - Simple chart entry

- Most onerous to physicians

- Most effective single intervention
  - McGowan and Finland. J Infect Dis 1974;130:165-8
  - Recco et al. JAMA 1979;241:2283-6
PRIOR APPROVAL: MICROBIOLOGICAL OUTCOMES

- Prior approval for selected parenteral agents
- Antimicrobial expenditures decreased 32%
- Susceptibilities to all β-lactam and fluoroquinolone antibiotics increased
  - Most dramatic in ICUs
- No change in survival
- No change in LOS
- No delay in appropriate therapy

White AC et al. *Clinical Infectious Diseases* 1997;25:230-9
Prior Approval

- The most widely implemented and evaluated approach to improving in-patient antimicrobial use
- The one true hard stop intervention
- Very effective and very quickly effective
- Relatively easy to implement
- Labor intensive
- Requires subject matter expertise
- Can create ill-will among providers
- Can lead to quick burnout of approvers
Knowledge of Infectious Diseases

Knowledge of Patient

Knowledge of Antibiotics

Decision to Use Antibiotics

Choice of Antibiotics

Refine Choice of Antibiotics

Prospective Audit & Feedback

Physician’s Attitude

Availability of Antibiotics

Patient’s Attitude and Desires

Culture Results

Refine Choice of Antibiotics

Culture Results
Prospective Audit & Feedback Example

Parenteral antibiotic use, cost per 1000 patient-days, and Medicare Case Mix Index (MCCMI)

Measurable, Sustained Outcomes

Rates of CDI

Rates of Resistant Enterobacteriaceae

Stewardship Optimizes Patient Safety: Improved Use of Antibiotics

Cluster randomized trial over 10 months
• 6 IM teams received academic detailing regarding appropriate use of vancomycin, levofloxacin, piperacillin/tazobactam
• 6 IM teams received guidelines only

Evaluation of Postprescription Review and Feedback as a Method of Promoting Rational Antimicrobial Use: A Multicenter Intervention

Sara E. Cosgrove, MD, MS; Susan K. Seo, MD; Maureen K. Bolon, MD, MS; Kent A. Sepkowitz, MD; Michael W. Climo, MD; Daniel J. Diekema, MD; Kathleen Speck, MPH; Vidhya Gunaseelan, MS; Gary A. Noskin, MD; Loreen A. Herwaldt, MD; Edward Wong, MD; Trish M. Perl, MD, MSc, for the CDC Prevention Epicenter Program

- Quasi-experimental before-after study of postprescription review
- 5 academic medical centers
- Adults receiving at least 48 hrs of study antibiotics
# Results of Multicenter Intervention

## Table 1. Rate of Study and Total Antimicrobial (ABX) Use and Incidence Rate Ratios (IRR) in Each Study Period

<table>
<thead>
<tr>
<th></th>
<th>Hospital A</th>
<th>Hospital B</th>
<th>Hospital C</th>
<th>Hospital D</th>
<th>Hospital E</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABX-days/1,000 patient-days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study ABX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>419.56</td>
<td>574.37</td>
<td>509.03</td>
<td>615.59</td>
<td>519.85</td>
</tr>
<tr>
<td>Intervention</td>
<td>469.62</td>
<td>533.84</td>
<td>497.28</td>
<td>512.62</td>
<td>596.07</td>
</tr>
<tr>
<td>Follow-up</td>
<td>446.33</td>
<td>...</td>
<td>476.67</td>
<td>602.72</td>
<td>642.47</td>
</tr>
<tr>
<td>Total ABX</td>
<td>395.63</td>
<td>548.02</td>
<td>474.07</td>
<td>522.25</td>
<td>473.46</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>443.30</td>
<td>484.01</td>
<td>460.80</td>
<td>421.42</td>
<td>560.87</td>
</tr>
<tr>
<td>Follow-up</td>
<td>397.36</td>
<td>...</td>
<td>425.20</td>
<td>500.57</td>
<td>605.77</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study ABX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention vs baseline</td>
<td>1.12 (1.05–1.19)</td>
<td>0.93 (0.88–0.98)</td>
<td>0.98 (0.91–1.04)</td>
<td>0.83 (0.79–0.88)</td>
<td>1.14 (1.08–1.22)</td>
</tr>
<tr>
<td>Intervention vs follow-up</td>
<td>0.95 (0.89–1.01)</td>
<td>...</td>
<td>0.96 (0.90–1.02)</td>
<td>1.18 (1.12–1.24)</td>
<td>1.08 (1.01–1.15)</td>
</tr>
<tr>
<td>Total ABX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention vs baseline</td>
<td>1.12 (1.06–1.18)</td>
<td>0.88 (0.85–0.92)</td>
<td>0.97 (0.92–1.03)</td>
<td>0.81 (0.77–0.84)</td>
<td>1.18 (1.13–1.25)</td>
</tr>
<tr>
<td>Intervention vs follow-up</td>
<td>0.90 (0.85–0.95)</td>
<td>...</td>
<td>0.92 (0.87–0.97)</td>
<td>1.19 (1.14–1.24)</td>
<td>1.08 (1.03–1.13)</td>
</tr>
</tbody>
</table>

**Note.** CI, confidence interval.

*Hospital B lacks follow-up data because the intervention was continued as hospital policy.*
Conclusions

- Postprescription review and feedback intervention most effective in institutions with established ASPs
  - Institutional support
  - Dedicated resources
- Acceptance rates equal
  - Greater case-finding and intervention
  - Increased contact with healthcare providers
Knowledge of Infectious Diseases

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COMPREHENSIVE AND COMPUTER-ASSISTED PROGRAMS
A COMPUTER-ASSISTED MANAGEMENT PROGRAM FOR ANTIBIOTICS
AND OTHER ANTIINFECTIVE AGENTS

R. Scott Evans, Ph.D., Stanley L. Pestotnik, M.S., R.Ph., David C. Classen, M.D., M.S., Terry P. Clemmer, M.D.,
Lindell K. Weaver, M.D., James F. Orme, Jr., M.D., James F. Lloyd, B.S., and John P. Burke, M.D.

NEJM 1998;338:232
**Table 1. Patient-Specific and Disease-Specific Issues Addressed by the Computerized Antiinfectives-Management Program.**

Monographs for antiinfective agents in formulary
5-Year antibiograms
Patient infections in the previous 5 years
Outpatient models for treatment of infections
Costs of antiinfective agents
Review of radiologic, pathological, and laboratory findings
Alternative therapies
Patient allergies
Alerts, suggestions, and interpretation regarding laboratory-test results
Contraindications
Alerts and suggestions regarding dose, route, and duration of therapy
Drug–drug interactions
Drug—laboratory-test interactions
Drug–nutrient interactions
Drug-therapy omission
Indication for drug use
Therapeutic duplication
Pharmacokinetic consultation

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**IHC ANTIBIOTIC ASSISTANT & ORDER PROGRAM**

00000000 Doc, John Q. E615 77yr M Dx: PANCREATITIS
Max 24hr WBC = 26.3 (21.1) Admit: 06/21/96.17.50 Max 24hr Temp = 38.3 (37.8)
RENAL FUNCTION: Impaired, CrCl = 28, Max 24hr Cr = 2.0 (2.2) IBW: 77kg
Patient’s Diff shows a left shift, Max 24hr Bands = 20 (8)
ANTIBIOTIC ALLERGIES: Oftoxacin
CURRENT ANTIBIOTICS:
1. 07/14/96.17.23 AMPHOTERICIN B, VIAL 45 Q 24hrs
2. 07/18/96.12.19 VANCOMYCIN (VANCOCIN), VIAL 1000 Q 72hrs
Total amphotericin given = 181mg

**IDENTIFIED PATHOGENS**

<table>
<thead>
<tr>
<th>SITE</th>
<th>COLLECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus</td>
<td>T-Tube 07/17/96.10.57</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Blood 07/17/96.10.28</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Abdomen 07/14/96.06.23</td>
</tr>
</tbody>
</table>

**ABX SUGGESTION**

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>ROUTE</th>
<th>INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin *1000mg</td>
<td>IV</td>
<td>*q72h (infuse over 1hr)</td>
</tr>
<tr>
<td>Amphotericin B 45mg</td>
<td>IV</td>
<td>q24h (infuse over 2-4hr)</td>
</tr>
</tbody>
</table>

Suggested Antibiotic Duration: 28 days

* Adjusted based on antibiotics renal function

<1> Micro, <2> Organism Suscept, <3> Drug Info, <4> Explain Logic, <5> Empiric Abx
<6> Abx Hx, <7> ID Rnds, <8> Lab/Abx Levels, <9> Xray, < + or F12 > Change Patient
<Esc> EXIT, <F1> Help, <0> User Input, <.> Outpatient Modes

**ORDERS:** < *> Suggested Abx, < Enter > Abx List, < / > D/C Abx, < -> Modify Abx

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*Figure 1. Example of the Type of Information Initially Displayed When the Computerized Antiinfectives-Management Program Is Used.*

Dx denotes diagnosis, max maximal, WBC white-cell count, CrCl creatinine clearance, Cr serum creatinine, IBW ideal body weight, Diff differential, arrows direction of change, IV intravenous, Abx antiinfective, Hx history, ID Rnds infectious-disease rounds, Lab laboratory, and D/C discontinue.
Computerized Antibiotic Assistant

**Significant reductions in:**

- Orders for drugs with reported allergies (35 vs. 146)
- Excess drug dosages (87 vs. 405)
- Antibiotic-susceptibility mismatches (12 vs. 206)
- Mean number of days of excessive dosages (2.7 vs. 5.9)
- Adverse events (4 vs. 28)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PREINTERVENTION PERIOD</th>
<th>INTERVENTION PERIOD</th>
<th>Regimen Followed</th>
<th>Regimen Overridden</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS - ICU (days)</td>
<td>4.9</td>
<td>2.7</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Total LOS (days)</td>
<td>12.9</td>
<td>10.0</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Cost of antiinfective ($)</td>
<td>340</td>
<td>102</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>Total cost ($)</td>
<td>35,283</td>
<td>26,315</td>
<td>44,865</td>
<td></td>
</tr>
</tbody>
</table>

GUIDELINES FOR ANTIMICROBIAL THERAPY

WEB ADDRESS

www.uphs.upenn.edu/antibiotics
Clinical Outcomes

UPHS ECONOMIC OUTCOMES
RANDOMIZED CONTROLLED TRIAL

Annual savings (600 interventions/month)

- Antibiotics: $302,400.00
- Infx-assoc costs: $533,000.00
- Total costs: $4,277,000.00
You can’t always get what you want...
But if you try sometime, you just might find, you get what you need!!
Impact Analysis
Antimicrobial Stewardship at a Large Tertiary Care Academic Medical Center: Cost Analysis Before, During, and After a 7-Year Program

Harold C. Standiford, MD;¹² Shannon Chan, PharmD;³ Megan Tripoli, BA;¹ Elizabeth Weekes, PharmD;⁴ Graeme N. Forrest, MBBS⁵
Stewardship Decreases Costs

Program Start
Pharmnet Implementation
CPMOE Program Ends

Stewardship Decreases Costs
Duration of Therapy
The clinical use of penicillin observations in one hundred cases

Martin Henry Dawson, M.D.
And
Gladys L. Hobby, Ph.D.
New York

of cases of this disease was therefore abandoned until such time as larger supplies might become available. In the light of subsequent work it became obvious that the amount of penicillin given in this early group of cases was totally insufficient to secure a significant result.

During this stage of the investigation 3 cases of acute pneumococcic endocarditis came under observation. 

Since it was known that streptococci were present in

prompt in 2 and more gradual in the other 2. In general the results were satisfactory with doses of 10,000 units every four hours for one and a half to two days, but in 1 instance there was a dramatic response with a dose of 5,000 units every three hours for one and a half days.
TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN

Manson Meads, M.D.,† H. William Harris, M.D.,‡ and Maxwell Finland, M.D.§

With the technical assistance of Clare Wilcox

Boston

---

**Table 2. Average Total Dosage of Penicillin and Duration of Treatment in Recovered Cases.**

<table>
<thead>
<tr>
<th>Type of Case</th>
<th>Average Total Dosage of Penicillin</th>
<th>Average Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>units</td>
<td>hrs.</td>
</tr>
<tr>
<td>Group I</td>
<td>411,000</td>
<td>86</td>
</tr>
<tr>
<td>Group II</td>
<td>728,000</td>
<td>162</td>
</tr>
<tr>
<td>Severity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>317,000</td>
<td>66</td>
</tr>
<tr>
<td>Grade 3</td>
<td>477,000</td>
<td>107</td>
</tr>
<tr>
<td>Grade 4</td>
<td>735,000</td>
<td>148</td>
</tr>
<tr>
<td>All cases</td>
<td>507,000</td>
<td>107</td>
</tr>
</tbody>
</table>
Duration of Antibiotics

• Some studies indicate that shorter courses of antibiotics are sufficient
  – Ventilator associated pneumonia
  – Community acquired pneumonia
  – Septic arthritis

• Regardless, duration of antibiotics in many cases longer than most would consider sufficient
  – Average duration of antibiotics for SSTI is 14 days (range 10-16 days)
  – Average duration for VAP is 15 days (range 10-21 days)

Hayashi, CID, 2011.
Peltola, CID 2009.
Treatment of VAP

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

- 8 day course equal to 15 day course in RCT

Chastre J. JAMA 2003;290:2588
Mathematical Modeling of ASP Interventions

A. Mathematical model

B. Fewer uninfected patients are prescribed antimicrobials (FP)

The duration of treatment is shortened (SD)

Fewer uninfected treated patients are prescribed the antimicrobial (AT)

Penn Medicine
Mathematical Modeling of ASP Interventions


Fraction of uninfected patients prescribed drugs

Mean duration of treatment, $1/\tau_1$

Fraction of treatment with ciprofloxacin, $\omega_2$
Impact on Antimicrobial Resistance
Impact of ASPs on Antimicrobial Resistance

Ecological Data

- Changes in antimicrobial use are paralleled by changes in the prevalence of resistance
- Antimicrobial resistance is more prevalent in healthcare-associated bacterial infections
- Patients with infections caused by MDROs are more likely to have received prior antimicrobials
- Hospital units with highest antimicrobial use also have highest resistance rates
- Increased duration of exposure (time at risk) increases likelihood of colonization with MDRO
Impact of ASPs on Antimicrobial Resistance

Epidemiological Data

- Majority of data from control of outbreaks
  - CDI
  - ESBL
  - VRE

- Limited data demonstrating impact on endemic resistance
POOR STUDY DESIGN ISSUES

- Selection biases
- Insufficient power
- Varying duration of intervention
- Failure to deal with confounders
  - Cause of resistance is multifactorial
  - Community vs. nosocomial pathogens
  - Multiple concurrent control measures
  - Colonization pressure

Generalizability
- Bug/drug combinations
- Setting
Can Antimicrobial Stewardship Limit Resistance?

Best Evidence

- Decreased CDI
- Decreased resistant GNB
- Decreased VRE
- Decreased LOS (particularly in the ICU)

Carling et al. ICHE 2003;24:699-706
Khan et al. J Hosp Infect 2004;54:104-8
Singh et al. Am J Respir Crit Care Med 2000;162:505-11
Impact of Changes in Antibiotic Prescribing on CDI in England

- 55% of all CDI caused by NAP1/027
- Among all CDI: 17% assoc. w Ceph
- 12% assoc. w FQ

- 36% of all CDI caused by NAP1/027
- Among all CDI: 12% assoc. w Ceph
- 4% assoc. w FQ

- 21% of all CDI caused by NAP1/027
- Among all CDI: 10% assoc. w Ceph
- 4% assoc. w FQ

http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1179745282388
Conclusions: *C. difficile* as an ASP Endpoint

- Data is compelling
- As much as 60% of healthcare-associated CDI may be attributable to antibiotic use
- Many published studies, using good methods, show an association between reduced antibiotic use and reduced *C. difficile* infections
- Results can be demonstrated within a year
- Targeting key antibiotics can be very effective
  - Fluoroquinolones
  - Cephalosporins
There are many published studies looking at the impact of reductions in antibiotic use on resistance.

Most of them do show favorable impacts:
- Reduced use leads to reduced resistance
- Could be publication bias
- Commonly in an outbreak setting

Some common limitations
Overall Impressions

- The data supporting reducing antibiotic use as a way to impact resistance are not as weak as I thought.
- Some studies are pretty compelling
  - CRE
- Few studies look at the impact of stewardship interventions on resistance among patients who were actually eligible to get the intervention
  - Case-case-control studies
Antimicrobial Stewardship and CRE

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRE vs uninfected</th>
<th>ESBL vs uninfected</th>
<th>Susceptible vs uninfected</th>
<th>CRE vs ESBL</th>
<th>CRE vs susceptible</th>
<th>CRE vs all controls combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
<td>OR (95% CI) P</td>
</tr>
<tr>
<td>Any antibiotic exposure in previous 3 months</td>
<td>11.4 (2–64.3) .006</td>
<td>1.7 (0.7–4.1) .24</td>
<td>5.2 (1.4–19.4) .015</td>
<td>12.3 (3.3–45) &lt;.001</td>
<td>7.1 (1.9–25.8) .003</td>
<td></td>
</tr>
<tr>
<td>Permanent residency in institution</td>
<td>1.04 (0.2–4.5) .96</td>
<td>1.3 (0.5–3.6) .56</td>
<td>0.15 (0.05–0.5) .002</td>
<td>2.1 (1–4.2) .05</td>
<td>5.3 (2.1–12.9) &lt;.001</td>
<td>2.6 (1.3–5.3) .01</td>
</tr>
<tr>
<td>Isolation of resistant bacteria in previous 6 months</td>
<td>15.3 (4.2–55.6) &lt;.001</td>
<td>8.25 (2.7–25.7) &lt;.001</td>
<td>6.6 (1.9–23.3) .003</td>
<td>1.7 (0.7–4.7) .2</td>
<td>1.8 (0.7–4.7) .33</td>
<td></td>
</tr>
<tr>
<td>Dependent functional status in background</td>
<td>1.4 (0.5–4.4) .55</td>
<td>5.6 (2.1–14.7) .001</td>
<td>2.6 (1.1–6.4) .03</td>
<td>2.0 (0.7–6.2) .2</td>
<td>1.6 (0.6–4) .33</td>
<td></td>
</tr>
<tr>
<td>ICU stay in previous 3 months</td>
<td>3.9 (1.3–12.4) .02</td>
<td>5.2 (2.1–13.2) .001</td>
<td>3.0 (1.2–7.2) .02</td>
<td>1.6 (0.6–4) .34</td>
<td>1.36 (0.7–2.7) .37</td>
<td></td>
</tr>
<tr>
<td>Recent (6 months) invasive procedure</td>
<td>4.2 (1.2–15) .03</td>
<td>1.2 (0.4–3.4) .76</td>
<td>3.2 (1.3–8) .01</td>
<td>2.8 (1.1–7.6) .04</td>
<td>2.7 (1.1–7.1) .04</td>
<td></td>
</tr>
<tr>
<td>Charlson weighted index comorbidity ≥3</td>
<td>3.1 (0.8–11.8) .1</td>
<td>1.1 (0.4–2.7) .87</td>
<td>2.2 (0.94–5) .07</td>
<td>2.4 (1.03–5.6) .04</td>
<td>4.8 (1.9–12.5) .001</td>
<td></td>
</tr>
</tbody>
</table>

Note. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

a If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.
b Part of the case-case-control analysis.
c Includes methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, ESBL-producing Enterobacteriaceae, Acinetobacter baumannii, and Pseudomonas aeruginosa.

# Antimicrobial Stewardship and CRE

## Table 3. Six separated multivariable models of risk factors for Enterobacteriaceae isolation, including enforcement of cephalosporin exposure into models (Detroit Medical Center, MI, USA, September 2008–September 2009).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRE versus uninfected</th>
<th>ESBL versus uninfected</th>
<th>Susceptible versus uninfected</th>
<th>CRE versus ESBL</th>
<th>CRE versus susceptible</th>
<th>CRE versus all controls combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
<td>OR (95% CI) p-value</td>
</tr>
<tr>
<td>Cephalosporin exposure in previous 3 months</td>
<td>3.6 (1.4–8.8) 0.006</td>
<td>1.8 (1.1–3.2) 0.03</td>
<td>0.8 (0.5–1.4) 0.4</td>
<td>1.7 (0.8–3.9) 0.18</td>
<td>4.9 (2.1–11.4) &lt;0.001</td>
<td>4.7 (2.0–11.0) &lt;0.001</td>
</tr>
<tr>
<td>Permanent residency in institution</td>
<td>1.0 (0.5–1.8) 0.95</td>
<td>0.9 (0.6–1.5) 0.7</td>
<td>0.6 (0.3–1.1) 0.08</td>
<td>1.5 (0.8–2.6) 0.21</td>
<td>1.8 (1.0–3.3) 0.08</td>
<td>1.7 (0.9–3.1) 0.09</td>
</tr>
<tr>
<td>Isolation of resistant bacteria in previous 6 months*</td>
<td>1.9 (1.0–3.7) 0.06</td>
<td>1.6 (0.9–2.6) 0.09</td>
<td>1.6 (0.9–2.6) 0.1</td>
<td>1.4 (0.8–2.5) 0.3</td>
<td>1.4 (0.8–2.6) 0.27</td>
<td>2.0 (1.1–3.6) 0.03</td>
</tr>
<tr>
<td>Dependent functional status in background</td>
<td>1.1 (0.5–2.4) 0.8</td>
<td>2.0 (1.0–4.0) 0.04</td>
<td>1.5 (0.9–2.4) 0.2</td>
<td>0.6 (0.3–1.2) 0.17</td>
<td>0.7 (0.3–1.4) 0.3</td>
<td>0.6 (0.3–1.3) 0.2</td>
</tr>
<tr>
<td>ICU stay in recent 3 months</td>
<td>1.2 (0.7–2.0) 0.6</td>
<td>1.5 (0.9–2.5) 0.09</td>
<td>1.3 (0.8–2.1) 0.3</td>
<td>0.9 (0.5–1.6) 0.8</td>
<td>1.0 (0.6–1.7) 0.9</td>
<td>1.1 (0.6–1.8) 0.8</td>
</tr>
<tr>
<td>Recent (6 months) invasive procedure</td>
<td>1.9 (0.8–4.6) 0.14</td>
<td>1.0 (0.6–1.7) 0.9</td>
<td>2.0 (1.1–3.4) 0.02</td>
<td>1.9 (0.8–4.3) 0.14</td>
<td>1.1 (0.5–2.5) 0.8</td>
<td>1.9 (0.8–4.3) 0.15</td>
</tr>
<tr>
<td>Charlson's combined condition score ≥4</td>
<td>1.4 (0.6–3.1) 0.42</td>
<td>1.0 (0.6–1.7) 0.9</td>
<td>0.8 (0.5–1.3) 0.5</td>
<td>1.8 (0.8–4.2) 0.15</td>
<td>1.7 (0.8–3.8) 0.2</td>
<td>2.2 (1.0–4.9) 0.06</td>
</tr>
</tbody>
</table>

*Includes methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, Acinetobacter baumannii, Pseudomonas aeruginosa and ESBL-producing Enterobacteriaceae.
CRE: Carbapenem-resistant Enterobacteriaceae; ESBL: Extended-spectrum β-lactamase-producing Enterobacteriaceae; ICU: Intensive-care unit; OR: Odds ratio.

Conclusions

- Antimicrobial stewardship interventions can arrest outbreaks of MDROs
  - CDI
  - ESBL
  - VRE

- Overall data demonstrating impact on antimicrobial resistance is improving
  - Correct study design critical
  - Must study impact on patients eligible to receive intervention

- Fewer data supporting effect of ASPs on endemic resistance
  - Impact on antibiogram unlikely to be an effective outcome measure

- Prior approval may be a more effective AS intervention with respect to preventing emergence of antimicrobial resistance
Environments Where Antibiotic Resistance Develops and Their Relationships

Adapted from B. Murray
Antibiotic Use in the United States

- 70% Nontherapeutic use - Livestock
- 6% Therapeutic use - Livestock
- 9% Therapeutic use - Humans
- 15% Other (soaps, pesticides, pets, etc.)

Union of Concerned Scientists, January 2001