Antibiotic Stewardship in Primary Care
Puerto Rico ACP 2020

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Disclosures for speaker:

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• No relevant financial disclosures:
  • Daniel C. DeSimone, MD

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  • None
Learning Objectives
Upon conclusion of this program, participants should be able to:

• Discuss the issues surrounding antimicrobial resistance and lack of new ABX development
• Describe the underlying principles of antimicrobial stewardship
• Discuss common outpatient ID syndromes and appropriateness of ABX therapy
Background

• 2002 survey: 1.7 million healthcare acquired infections (100,000 deaths) in the US annually.
  • ~$6.5 billion in annual healthcare expenditure

• Infection with a multidrug resistant (MDR) organism =
  • Increased cost
  • Longer length of hospitalization
  • Increased risk of mortality

• Antibiotic-resistant pathogens in the US result in:
  • An annual cost of $21-34 billion dollars
  • More than 8 million hospital days annually
Background

• The rate of new antimicrobial development has slowed significantly as of late.
  • FDA approval rate of new antimicrobial agents decreased by 56% between 1983 and 2002.
Background:

- **Sir Alexander Fleming:**
  - Discovered penicillin in 1928
  - Nobel Prize in Physiology/Medicine in 1945
  - New York Times article from 1945:
    - “…the microbes are educated to resist penicillin and a host of penicillin-fast organisms are bred out…In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin resistant organism. I hope that this evil can be averted.”

Infect Control Hosp Epidemiol 2012;33(4):322-327
Antimicrobial stewardship

- Coordinated interventions designed to promote the optimal use of antimicrobial agents including
  - Choice
  - Dosing
  - Route
  - Duration
Goals

- Reduction in inappropriate use of antimicrobials and optimization of appropriate use (i.e. drug, dose, route, frequency, and duration)

- Primary goals:
  - Optimize clinical outcomes
    - Improved patient outcomes
    - Shorter length of stay (LOS)
  - Minimizing unintended consequences
    - i.e. toxicity, emergence of resistance, and selection of resistant organisms.

- Secondary
  - Cost-savings
    - Pharmacy (Literature reports 22-36% reduction in antimicrobial use)
    - Other (i.e. length of stay)
The Team:

- Recommended Team:
  - ID Pharmacist
  - ID Physician
  - Microbiology
  - Infection Control
  - Information Systems Specialist
  - Administration
  - Departmental Stakeholders
Outpatient Antimicrobial Stewardship:

Community Antibiotic Prescriptions per 1,000 Population by State - 2017

Data source: IQVIA Xponent 2017

Antimicrobial Resistance: *E. coli*

**Antibiotic Resistance**

![Antibiotic Resistance of *Escherichia coli* in United States](image)

**Antibiotic Resistance of *Escherichia coli***

![Antibiotic Resistance of *Escherichia coli*](image)

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**Data includes** aggregated resistance rates for isolates (includes intermediate resistance) from blood and cerebrospinal fluid (i.e., invasive) from inpatients of all ages. Because of differences in scope of collections and testing methods, caution should be exercised in comparing across countries. For more details see [methodology](https://resistancemap.cddep.org/AntibioticResistance.php). Date accessed: 12/17/2019
Concerning Threats

- ERYTHROMYCIN-RESISTANT GROUP A STREPTOCOCCUS
- CLINDAMYCIN-RESISTANT GROUP B STREPTOCOCCUS

Urgent Threats

- CARBAPENEM-RESISTANT ACINETOBACTER
- CLOSTRIDIODES DIFFICILE
- CARBAPENEM-RESISTANT ENTEROBACTERIACEAE
- DRUG-RESISTANT NEISSERIA GONORRHOEAE

Serious Threats

- DRUG-RESISTANT CAMPYLOBACTER
- DRUG-RESISTANT CANDIDA
- ESBL-PRODUCING ENTEROBACTERIACEAE
- VANCOMYCIN-RESISTANT ENTEROCOCCI
- MULTIDRUG-RESISTANT PSEUDOMONAS AERUGINOSA
- DRUG-RESISTANT NONTYPHOIDAL SALMONELLA
- DRUG-RESISTANT SALMONELLA SEROTYPE TYPHI
- DRUG-RESISTANT SHIGELLA
- METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS
- DRUG-RESISTANT STREPTOCOCCUS PNEUMONIAE
- DRUG-RESISTANT TUBERCULOSIS

CDC. Antibiotic Resistance Threats in the US, 2019: U.S. Department of Health and Human Services, CDC; 2019
No ESKAPE!

- ESKAPE Pathogens
  - *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* species

- Increasing resistance
  - Pan-ABX resistance has been identified (P. aeruginosa / A. Baumanii)
    - New resistance mechanisms: Metalo-beta-lactamase 1 (NDM-1)
  - Decreasing antibiotic development
    - CDC, FDA, IDSA, NIH, and Congress all working together to encourage development of new drugs
Resistance: A few basic truths

- Change in antimicrobial use = change in resistance patterns
- Resistance is more common in healthcare/hospital acquired infections vs. community acquired
- Patients with resistant, healthcare associated infections are more likely to have received previous antimicrobial therapy than control patients
- Even within an institution, higher antimicrobial use = higher rates of resistance in hospital-acquired infections
- The longer a patient is exposed to an antimicrobial the more likely they will become colonized with an organism resistant to that antimicrobial
Antimicrobial Stewardship:

- **Primary Interventions:**
  - Prospective audit with intervention and feedback
  - Formulary restriction

- **Secondary Interventions:**
  - IV to PO switch
  - De-escalation
  - Guidelines/clinical pathways
  - Ordersets/Order forms
  - Education

- **5 D’s of Antimicrobial Stewardship:**
  - Diagnosis
  - Drug regimen (empiric)
  - Dosing
  - De-escalation (targeted)
  - Duration of therapy

CID 2007;44(2):159-177
Exp Opin Pharmacother 2008;9:561-75
Core Elements of Outpatient Antimicrobial Stewardship:

**CDC Core Elements:**

1. Identifying an antimicrobial stewardship leader
2. Establishing an annual antimicrobial stewardship goal
3. Implementing evidence-based practice guidelines related to the antimicrobial stewardship goal
4. Providing clinical staff with educational resources related to the antimicrobial stewardship goal
5. Collecting, analyzing, and reporting data related to the antimicrobial stewardship goal

**The Joint Commission Standard Elements:**

- Identifying an antimicrobial stewardship leader
- Establishing an annual antimicrobial stewardship goal
- Implementing evidence-based practice guidelines related to the antimicrobial stewardship goal
- Providing clinical staff with educational resources related to the antimicrobial stewardship goal
- Collecting, analyzing, and reporting data related to the antimicrobial stewardship goal

R³ Report 2019;23:1-3
Outpatient Antimicrobial Stewardship:

• Scoping the problem:
  • Estimated 80-90% of human antibiotics = outpatient
  • In 2017:
    • 258.2 million antibiotic prescriptions written
    • 30% unnecessary: 77.46 million prescriptions
    • 50% inappropriate/unnecessary: 129.1 million prescriptions

Age:
<20 y/o: 23.4%
≥20 y/o: 76.4%

Sex:
Male: 39.1%
Female: 60.9%

Top Classes:
1) Penicillins (23.7%)
2) Macrolides (17.3%)
3) Cephalosporins (14%)
4) Fluoroquinolones (10.3%)
5) Beta-lactam, increased activity (9.5%)

Amoxicillin, azithromycin, Augmentin, cephalexin, and Bactrim accounted for ~64% of all Rx.

Region:
West: 17.3%
Northeast: 18.2%
Midwest: 22%
South: 42.5%

CDC Annual Outpatient Antibiotic Prescription Report. 2017
FUNDING TO STATE HEALTH DEPARTMENTS

**Rapid Detection & Response:** State, territory, and local public health partners fight antibiotic resistance in healthcare, the community, and food. Programs use the AR Lab Network to rapidly detect threats and implement prevention, response, and antibiotic stewardship to stop the spread of resistant germs.

With 2018 funds, Puerto Rico implemented antibiotic stewardship programs at more than 65% of hospitals. Using community AR surveillance data, Puerto Rico identified populations at increased risk for infection due to incorrect use of antibiotics and piloted an educational program to prevent inappropriate antibiotic use in outpatient settings. As of July 2019, Puerto Rico has engaged 60% of the ambulatory care centers selected to participate in the pilot program.

**Natural Disasters** can increase the risk for injuries and infections.

With 2019 funds, the Puerto Rico Department of Health hired nurses to support healthcare-associated infection activities in hurricane-damaged hospitals, safety officers to conduct facility infrastructure assessments, and regional nurses to support facilities. CDC provided training and assessment materials to newly hired nurses. Twenty-two facility assessments were completed, eleven training plans were developed, and twenty staff were trained for Certification of Infection Control.

**Food Safety** projects protect communities by rapidly identifying drug-resistant foodborne bacteria to stop and solve outbreaks and improve prevention.

Puerto Rico uses whole genome sequencing to track and monitor local outbreaks of *Listeria, Salmonella, Campylobacter,* and *E. coli* and uploads sequence data into PulseNet for nationwide monitoring of outbreaks and trends. In Fiscal Year 2020, Puerto Rico will continue monitoring these isolates for resistance genes. When outbreaks are detected, local CDC-supported epidemiologists investigate the cases to stop spread.
Acute Bronchitis

• Rhinovirus, enterovirus, influenza A/B, parainfluenza, coronavirus, metapneumovirus, RSV

• Bacteria (1-10%). Atypical bacteria, such as M. pneumoniae, C. pneumoniae, B. pertussis are rare
Strategies to reduce antibiotic use

• Use delayed prescription strategies
• Describe the infection as a viral illness or chest cold
• Discuss the expected course of illness and cough duration (2-3 weeks)
• Explain that antibiotics do not significantly shorten illness duration and are associated with adverse effects and resistance
• Non-antibiotic medications: dextromethorphan, guaifenesin, beta$_2$ agonists only if wheezing
Indications for Antimicrobial Use

• Influenza: Oseltamivir

<table>
<thead>
<tr>
<th>Information for Specific High Risk Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 65 Years and Older</td>
</tr>
<tr>
<td>Pregnant Women</td>
</tr>
<tr>
<td>Young Children</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
</tbody>
</table>

• Pertussis: Macrolides
COPD Exacerbation

• Outpatients with a moderate or severe exacerbation

• Having at least 2 of the following 3 symptoms:
  • Increased dyspnea
  • Increased sputum volume
  • Increased sputum purulence

• Antibiotic coverage: S. pneumoniae, H. influenzae, M. catarrhalis
  • Azithromycin, doxycycline, TMP/SMX, cefdinir
For mild to moderate COPD exacerbations, no difference between short course (≤5 days) and long course (≥7) days of antibiotic therapy

Thorax. 2008 May;63(5):415-22
Pneumonia

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia
An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America
## Updates

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>2007 ATS/IDSA Guideline</th>
<th>2019 ATS/IDSA Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide monotherapy</td>
<td>Strong recommendation for outpatients</td>
<td>Conditional recommendation for outpatients based on resistance</td>
</tr>
<tr>
<td>Empiric therapy for severe CAP</td>
<td>Beta-lactam/macrolide and beta-lactam/fluoroquinolone given equal weighting</td>
<td>Stronger evidence in favor of beta-lactam/macrolide combination</td>
</tr>
<tr>
<td>Use of HCAP Category</td>
<td>Accepted as per 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines</td>
<td>Abandon the category and focus on local epidemiology and validated risk factors to determine need for MRSA or <em>P. aeruginosa</em></td>
</tr>
</tbody>
</table>
Antibiotics Recommended for Empiric Treatment

Adults with comorbidities (chronic heart, lung, liver, renal disease, diabetes mellitus, alcoholism, malignancy, or asplenia):

• Combination therapy with amoxicillin/clavulanate or a cephalosporin PLUS macrolide or doxycycline

  OR

• Monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin)
What Is the Appropriate Duration of Antibiotic Treatment?

• Until the patient achieves stability and for no less than 5 days

• Duration of therapy due to suspected or proven MRSA or *Pseudomonas aeruginosa* should be 7 days
URINARY TRACT INFECTIONS
Asymptomatic Bacteriuria

• Pregnant women
  • Treatment reduces the risk of pyelonephritis and may reduce the risk of low birth weight and preterm labor

• Patients undergoing endoscopic urologic procedures associated with mucosal trauma
  • Substantial risk of postoperative sepsis
Asymptomatic Bacteriuria

• Screening and treatment **not** recommended for:
  • Infants and children
  • Healthy nonpregnant women of any age
  • Elderly persons living independently or in a long-term care facility
  • Diabetes
  • Renal transplant recipients >1 month after surgery
  • Patients with spinal cord injury
  • Patients with indwelling urinary catheters
Asymptomatic Bacteriuria

- Risk of prosthetic joint infection in treated vs untreated asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotics Events</th>
<th>Antibiotics Total</th>
<th>No antibiotics Events</th>
<th>No antibiotics Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordero–Ampuero 2013</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drekonja 2013</td>
<td>1</td>
<td>26</td>
<td>0</td>
<td>20</td>
<td>10.3%</td>
<td>2.33 [0.10, 54.42]</td>
<td></td>
</tr>
<tr>
<td>Sousa 2014</td>
<td>6</td>
<td>154</td>
<td>7</td>
<td>149</td>
<td>89.7%</td>
<td>0.83 [0.29, 2.41]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>181</td>
<td>170</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.92 [0.34, 2.53]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.37, df = 1 (P = 0.54); I^2 = 0%

Test for overall effect: Z = 0.16 (P = 0.88)

CID 2019; 68(10):e83-75
Duration of Treatment

MALE
- Nitrofurantoin 100 mg bid for 7 days
- TMP-SMX 160/800 mg bid for 7 days
- Cefdinir 300 mg bid for 7 days
- Limited data for fosfomycin use in men

FEMALE
- Nitrofurantoin 100 mg bid for 5 days
- TMP-SMX 160/800 mg bid for 3 days
- Cefdinir 300 mg bid for 5 days
- Fosfomycin 3 g once
Recurrent UTIs

- ≥2 infections in 6 months or ≥3 infections in a year
- Typically acute simple cystitis rather than complicated UTI
- Vast majority of recurrences of simple cystitis appear to be reinfections
Preventive Measures

- ↑ fluid intake (2-3 L/day)
- Avoid use of spermicidies
- Early postcoital voiding
- Wiping from front to back
- Vaginal estrogen for postmenopausal women
- Cranberry products
- Probiotics
- Methenamine salts (Hiprex)
- D-mannose
# Stewardship: Shorter = Better

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Short (d)</th>
<th>Long (d)</th>
<th>Result</th>
<th>#RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>3 or 5</td>
<td>7-14</td>
<td>Equal</td>
<td>9</td>
</tr>
<tr>
<td>VAP</td>
<td>8</td>
<td>15</td>
<td>Equal</td>
<td>2</td>
</tr>
<tr>
<td>Pyelo</td>
<td>7 or 5</td>
<td>14 or 10</td>
<td>Equal</td>
<td>7</td>
</tr>
<tr>
<td>Intra-abd</td>
<td>4</td>
<td>10</td>
<td>Equal</td>
<td>2</td>
</tr>
<tr>
<td>GNB Bacteremia</td>
<td>7</td>
<td>14</td>
<td>Equal</td>
<td>1*</td>
</tr>
<tr>
<td>AECB</td>
<td>≤5</td>
<td>≥7</td>
<td>Equal</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>5-6</td>
<td>10</td>
<td>Equal</td>
<td>4*</td>
</tr>
<tr>
<td>Chronic Osteomyelitis</td>
<td>42</td>
<td>84</td>
<td>Equal</td>
<td>2</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>14</td>
<td>28</td>
<td>Equal</td>
<td>1</td>
</tr>
<tr>
<td>Ortho Implant w/removal</td>
<td>28</td>
<td>42</td>
<td>Equal</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>AFx72 h</td>
<td>+ANC&gt;500</td>
<td>Equal</td>
<td>1</td>
</tr>
<tr>
<td>*P. vivax Malaria</td>
<td>7</td>
<td>14</td>
<td>Equal</td>
<td>1</td>
</tr>
</tbody>
</table>

*GNB bacteremia also in UTI/cIAI RCTs; 3 cellulitis RCTs equal, 1 (low dose oral flucox) ↑relapses; refs at [https://www.bradspellberg.com/shorter-is-better](https://www.bradspellberg.com/shorter-is-better)
Outpatient Antimicrobial Stewardship

• Antimicrobial resistance is a growing concern.

• Antibiotics in the outpatient care setting make up a bulk of human antibiotic use.

• Opportunity exists for optimization of outpatient antibiotic prescribing.

• The most common indications for outpatient antibiotic prescribing are:
  1. Respiratory tract infections
  2. Skin and soft tissue infections
  3. Genitourinary tract infections
Thank You

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