Antibiotic Resistance

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Clinical Pharmacy Specialists - Antimicrobial Stewardship
Disclosures

• The presenters do not have any financial interest in relation to this activity
Antibiotic Discovery

- One of the MOST significant advances of modern science
  - Millions of lives saved

- Medical revolution
  - Transplant, cancer treatment, childbirth...
  - Focus shift from diagnosis to treatment

Sir Alexander Fleming
- Nobel Prize 1945
- Discovery of penicillin

Marston H et al. JAMA. 2016;316(11):1193-1204
How Important are Antibiotics?

Antibiotics caused US deaths to decline by ~220 per 100,000 in 15 years

Sulfa

Penicillin

All other medical technologies reduced deaths by ~20 per 100,000 over the next 45 years

US Infection Death Rate per 100,000 population

1940 1960 1980
Pre-Antibiotic Era

“For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing that could be done beyond bed rest and good nursing care.”

Lewis Thomas, MD
- Albert Lasker Award winner
- Member of the National Academies of Science
- National Book Award
A Modern Scenario

- **Day 1:** Houston hospital – 2 year old boy, severe diarrhea, n/v, high fever
  - IV fluids, IV antibiotics, admitted

- **Day 3:** Cultures return positive for *Salmonella*
  - Highly resistant to common antibiotics
  - Dies from dehydration/septic shock

- **Day 4:** 28 year old expectant mother
  - Same symptoms, *Salmonella*, same result

- **Day 6:** 342 people are dead
  - 1000’s funnel into USA emergency rooms
  - 15 states widely impacted, isolated cases in numerous others, 27 cases reported in Canada and Mexico

- **Day 8:** Over 1700 deaths and 220K illnesses
  - Exports and travel from USA blocked
  - Milk distribution facility in Texas
  - Resistant to all antibiotics, hospitals can only provide supportive care
Could it Happen?

- In 1985, milk contaminated with *Salmonella typhimurium* infected more than 160,000 people across the Midwest USA.

- The ONLY thing separating the 1985 outbreak from this modern-day scenario is a fully antibiotic-resistant strain.

- Multi-drug resistant *Salmonella* species already exist, and represent a considerable public health threat.
Objectives

1. Examine factors associated with the development of antibiotic resistance (AR)
2. Assess the current epidemiology of clinically important AR organisms
3. Evaluate possible solutions targeting the problem of AR
4. Discuss novel agents recently approved with activity against AR organisms
EXAMINE FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ANTIBIOTIC RESISTANCE
Bacterial Genetics

- De novo mutations
  - *Staphylococcus aureus*
  - 10 generations in < 12 hours
  - 1 million progeny

- Each replication = opportunity for mutation
  - Emergence of genetic factors that contribute to AR

- Although naturally occurring resistance factors contribute….  
  - Antibiotic use selects for emergence
  - Therefore, human activity plays an important role in AR

Marston H et al. JAMA. 2016;316(11):1193-1204
Resistance Drivers

- Use of antibiotics is the single MOST important factor leading to resistance

- Antibiotics are among the most commonly prescribed drugs in human medicine

- Up to 50% of all antibiotics prescribed for people are not needed or are not optimally effective as prescribed

Marston H et al. JAMA. 2016;316(11):1193-1204
Pediatric Perspective

- Antibiotic usage in children is HIGH
  - 60% of hospitalized children receive an antibiotic

- One third of ALL pediatric prescriptions
  - ~49 million prescriptions, 21% of all ambulatory visits
  - Half of these prescriptions are prescribed for NON BACTERIAL infections (ex: upper respiratory tract)

- Leads to selective pressure
  - Direct relationship between consumption and resistance

Levy ER et al. Infect Control Hosp Epidemiol 2012;33:346
Hersh A et al. Pediatrics 2011;128:1053
More Consumption = More Resistance
Human Antibiotic Use by Country

Total antibiotic consumption in selected countries, 2000 and 2010

TCH Inpatient System (all hospitals):
Most Days of Therapy/1,000 Patient Days in 2018

Horizontal Black Lines Represent 25th, Median, & 75th Percentile.

Chart from PHIS Antibiotic Stewardship Report V2.
Inpatients <= 18 Yrs old; excludes normal newborns, Ob/Gyn, & Pav; includes mortalities
Agricultural Antibiotics

- USA: antibiotic use in animals represents 80% of TOTAL consumption
  - 74% administered in feed to promote growth
  - 62% of antibiotics used in animals are "medically important" compounds

- Evidence linking antibiotic consumption in animals to the existence of AR in humans
  - Colistin resistance gene (mcr-1) in China

Marston H et al. JAMA. 2016;316(11):1193-1204
Agricultural Antibiotic Use by Country

Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)
Perfect Storm

Resistant organisms

more broad spectrum antibiotic use

more resistant organisms
Lack of Antibiotic Development

- Limited duration of treatment
- Restrictions on use
- Potential for rapid AR
## Rapid Resistance

### Table: Antibiotics and Year of Approval or Introduction to Market

<table>
<thead>
<tr>
<th>Class</th>
<th>Antibiotic</th>
<th>Year of Approval or Introduction to Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>Penicillin</td>
<td>1942</td>
</tr>
<tr>
<td></td>
<td>Methicillin</td>
<td>1960</td>
</tr>
<tr>
<td></td>
<td>Cephalothin</td>
<td>1964</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin-clavulanic acid</td>
<td>1984</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Imipenem-cilastatin</td>
<td>1985</td>
</tr>
<tr>
<td>Amphenicols</td>
<td>Chloramphenicol</td>
<td>1950</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Tetracycline</td>
<td>1953</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Streptomycin</td>
<td>1946</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin</td>
<td>1952</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>1958</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Nalidixic acid</td>
<td>1964</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Quinupristin-dalfopristin</td>
<td>1999</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>2000</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>Daptomycin</td>
<td>2003</td>
</tr>
</tbody>
</table>

### Diagram: Years from Approval or Introduction to Market to First Clinical Report of Resistance

- 5 years from approval or introduction to market to first clinical report of resistance.

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Marston H et al. JAMA. 2016;316(11):1193-1204
Antibiotic use is the key driver for development of antibiotic resistance. In the USA, which of the following scenarios accounts for ~80% of total antibiotic use?

A) surgical procedures
B) growth promotion in animals raised for food
C) prophylaxis of opportunistic infections
D) outpatient visits to primary care providers
ASSESS THE CURRENT EPIDEMIOLOGY OF CLINICALLY IMPORTANT ANTIBIOTIC RESISTANT ORGANISMS
How Big of a Problem is AR Now?

- World Health Organization: top 3 threat to human life

- USA: yearly....
  - > 2 million illnesses
  - > 50 thousand deaths
  - > 8 million hospital days ($ 30 billion)

- Estimated by the year 2050:
  - More deaths annually than diabetes + cancer combined
# CDC: Antibiotic Resistant Threats (2013)

<table>
<thead>
<tr>
<th>Urgent Threats</th>
<th>Serious Threats</th>
<th>Concerning Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridioides difficile</em></td>
<td>Multi Drug Resistant (MDR) <em>Acinetobacter</em></td>
<td>Vancomycin resistant <em>Staphylococcus aureus</em> (VRSA)</td>
</tr>
<tr>
<td><em>Carbapenem resistant</em></td>
<td>Extended spectrum beta-lactamase (ESBL) producing <em>Enterobacteriaceae</em></td>
<td>Erythromycin resistant Group A <em>Streptococcus</em></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em> (CRE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-resistant <em>Neisseria gonorrhea</em></td>
<td>Vancomycin resistant <em>Enterococcus</em></td>
<td>Clindamycin resistant Group B <em>Streptococcus</em></td>
</tr>
<tr>
<td></td>
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<tr>
<td><em>MDR Pseudomonas</em></td>
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<td></td>
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<tr>
<td><em>Methicillin resistant</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (MRSA)</td>
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<td></td>
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<tr>
<td><em>Drug resistant</em></td>
<td></td>
<td></td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
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</tr>
</tbody>
</table>

- List is NOT all inclusive
- Center for Disease Control and Prevention (CDC) update expected in fall of 2019
Streptococcus pneumoniae

- Penicillin discovery to early 1970’s
  - Susceptible to all antibiotic classes

- South Africa: 1977-1978
  - Resistance outbreaks
  - Children with viral diseases (“prophylactic” antibiotics)
  - Medical curiosity to world-wide health problem

- Resistance concerns
  - Beta-lactams, macrolides, lincosamides, and fluoroquinolones
  - Annually: 1.2 million drug resistant infections and 7,000 deaths

CDC. Antibiotic Resistant Threats in the USA. 2013.
**S. pneumoniae Susceptibility**

- **USA (old breakpoints)**
  - Penicillin: 60% (S), 20% (I), 20% (R)

- **USA (new breakpoints - 2014)**
  - Penicillin (IV therapy, non-CNS): 95% (S), 3% (I), 2% (R)

- **TCH 2017 Antibiogram ("Total Patients")**

<table>
<thead>
<tr>
<th>Period, syndrome and route of administration</th>
<th>MIC µg/mL, by susceptibility category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before January 2008</td>
<td>Susceptible  Intermediate  Resistant</td>
</tr>
<tr>
<td>After January 2008 to present</td>
<td>&lt;0.06  0.12–1  &gt;2</td>
</tr>
<tr>
<td>For meningitis via intravenous route</td>
<td>&lt;0.06  None  &gt;0.12</td>
</tr>
<tr>
<td>For nonmeningitis syndrome</td>
<td>&lt;2  4  &gt;8</td>
</tr>
<tr>
<td>Via intravenous administration</td>
<td>&lt;0.06  0.12–1  &gt;2</td>
</tr>
<tr>
<td>Via oral administration</td>
<td></td>
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</tbody>
</table>

MIC: Minimum Inhibitory Concentration

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Active Bacterial Core Surveillance (ABCs): Emerging Infections Program Network. Streptococcus pneumoniae, 2014
Methicillin-resistant *Staphylococcus aureus*

- First described in Europe in 1961
  - Methicillin marketed in 1959
  - Drastic increase in both nosocomial and community acquired infections

- USA: 95,000 infections and 18,000 deaths per year due to MRSA
  - Among 4,000 patients with bacteremia
    - Patients with methicillin-susceptible isolate were 1.5 to 2x less likely to die than patients with MRSA

Klevens et al. JAMA. 2007;298(15):1763
Methicillin-resistant *Staphylococcus aureus*

- **Community Acquired MRSA**
  - Initially reported among injection drug users (1980’s)
    - Now the most common cause of skin/soft tissue infection in the USA
    - Pediatric incidence increasing?
    - 2017 TCH outpatient antibiogram: 73% methicillin-sensitive *S. aureus* (MSSA)
    - 78% MSSA
    - 22% MRSA

Pseudomonas sp.

- Found in soil, water, plants (*P. aeruginosa*)
  - Nosocomial and/or immunocompromised hosts
  - Estimated 7,000 infections per year (500 deaths)

- NHSN, USA (2011 to 2014):
  - 6th - hospital-acquired infections in general (7.3%)
  - 2nd - ventilator-associated pneumonia (VAP) (16.5%)
  - 3rd - catheter-associated UTI (CAUTI) (10.3%)

Pseudomonas sp. and Resistance

- USA: declining resistance trend, but still high
  - National cohort of CAUTI, VAP, and catheter-related bloodstream infections:
    - 22-26 % resistance for cefepime and ceftazidime
    - 16-19% for piperacillin/tazobactam
    - 30-33% for fluoroquinolones
    - 24-28% for carbapenems
    - 17-23 % for aminoglycosides

- TCH Perspective (2017 Antibiogram – “Total Patients”)
  - Only piperacillin/tazobactam falls below 90% susceptibility
N. gonorrhoeae

- Gram negative coccus occurring in pairs (diplococci)
  - Sexually transmitted or acquired congenitally

- Extremely common in the pre-antibiotic era
  - Antibiotics led to control in some populations
  - Still, one of the most common communicable diseases

- USA
  - Most common in adolescents and young adults
  - Estimated 550,000 infections in 2018
  - Rapid increase in AR in the USA
    - However, < 1% of all isolates with reduced ceftriaxone susceptibility (minimum inhibitory concentration ≥0.25 µg/mL)

History of discovered and recommended antimicrobials and evolution of resistance in Neisseria gonorrhoeae, including the emergence of genetic resistance determinants, internationally.
**N. gonorrhoeae: Current Treatment**

- **2015:** CDC - one regimen = ceftriaxone + azithromycin
  - Azithromycin susceptibility declined from 2013-2017

- **High Stakes:** looming public health crisis
  - Foundation of control is appropriate treatment
    - More complicated and costly regimens
    - Treatment failures and reproductive health consequences
  - 2017 – first ceftriaxone resistant isolate identified in North America (Canada)

Lefebvre B et al. Emerg Infect Dis. 2018 Feb;24(2)*
Carbapenem Resistant *Enterobacteriaceae* (CRE)

- **Enterobacteriaceae**
  - *E. coli*, *Klebsiella*, *Citrobacter*, *Enterobacter* etc. species
  - Variety of healthcare associated infections

- **Carbapenemms (extremely broad spectrum)**
  - **NOT covered**: MRSA, *Stenotrophomonas*, *Enterococcus* spp., atypicals
  - **Common uses**: Infections due to ESBL and other MDR organisms, life threatening infections/septic shock

- **CRE in the USA**
  - Over 9,000 infections per year and 600 deaths
High Mortality & Limited Treatment Options

- **General:** based on site & treatment strategy
  - 20 to 30%

- **Serious infections:** pneumonia or bacteremia
  - 40 to 50%

- **Other resistance present:** polymyxins & tigecycline
  - ≥ 60%

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CRKP = carbapenem resistant *Klebsiella pneumoniae*

CSKP = carbapenem susceptible *Klebsiella pneumoniae*
CRE: *K. pneumoniae* Carbapenemase (KPC)

2002

CRE: *K. pneumoniae* Carbapenemase (KPC)
Local CRE Incidence

Texas Children's Hospital: # of CRE Isolates Per Year

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<thead>
<tr>
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<tbody>
<tr>
<td>Value</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>19</td>
<td>32</td>
<td>21</td>
<td>16</td>
</tr>
</tbody>
</table>
Audience Question

According to the CDC ______________ is an urgent threat responsible for an estimated 550,000 infections in the USA in 2018, with ≤ 1% showing reduced ceftriaxone susceptibility. However, a ceftriaxone-resistant isolate was recently discovered in North America for the first time ever in 2017.

A) Streptococcus pneumoniae
B) Carbapenem resistant *Enterobacteriaceae*
C) Methicillin-resistant *Staphylococcus aureus*

*Neisseria gonorrhea*
EVALUATE POSSIBLE SOLUTIONS TARGETING THE PROBLEM OF AR
Strategic Planning

Local
- Antimicrobial Stewardship Programs
- Public education (i.e. Antibiotic Awareness Week)
- Promoting infection control and prevention, hand hygiene

National
- U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria
- White House Forum on Antibiotic Stewardship
- U.S. National Strategy for Combating Antibiotic-Resistant Bacteria
- Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Global
- Transatlantic Taskforce on Antimicrobial Resistance
- Antimicrobial Resistance Challenge
- United Nations General Assembly
- World Health Organization (WHO): World Antibiotic Awareness Week
Antimicrobial Stewardship

- Measure antibiotic prescribing
- Improve antibiotic prescribing so that antibiotics are only prescribed and used when needed
- Ensure prompt initiation of the right antibiotics when they are needed
- Ensure that the right drug, dose, and duration are selected
Effective Stewardship and Reductions in Antibiotic Resistance

- Retrospective controlled interrupted time-series study
  - Two academic hospitals – one with and one without a stewardship program
- Examined the effect of implementation of a hospital-based stewardship program on *E. coli* antibiotic resistance between 2008 and 2014
- Experimental group (stewardship program) showed a decrease in cephalosporin (-151 fewer DDDs) and fluoroquinolone (-44.5 fewer DDDs) use
- Significant improvement in the slope of *E. coli* resistance over time to fluoroquinolones and cephalosporins

DDD: defined daily dose

National Timeline for Implementing Antimicrobial Stewardship Programs

- **September 2014**
  - President Obama issues Executive Order 13676 to combat antibiotic-resistant bacteria.

- **March 2015**
  - CMS releases proposed CoP requiring antimicrobial stewardship.

- **June 2016**
  - The Joint Commission begins surveying hospitals for compliance with antimicrobial stewardship standards.

- **January 2017**
  - The Joint Commission releases requirements for ASPs.

- **2018**
  - All acute care hospitals participating in Medicaid/Medicare services must implement ASPs.

- **2020**
  - All health care delivery systems will demonstrate antimicrobial stewardship.

**ASPs, antimicrobial stewardship programs; CMS, Centers for Medicare & Medicaid Services; CoP, Conditions of participation.**

Centers of Disease Control and Prevention (CDC): AR Solutions Initiative

1. Preventing Infections and Preventing the Spread of Disease and Resistance
2. Tracking

3. Improving Antibiotic Prescribing and Use, “Stewardship”
4. Developing New Drugs and Diagnostics

CDC’s Four Core Actions
CDC’s Core Elements of Antibiotic Stewardship for Hospitals, Nursing Homes, and Outpatient Settings

2014 Hospitals
2015 Nursing Homes
2016 Outpatient
2017 Small & Critical Access Hospitals
Percentage of Hospitals Meeting all 7 Core Elements of Hospital Antibiotic Stewardship Programs* by State, 2017

Nationally, 76.4% of hospitals have met all 7 Core Elements (3,815 of 4,992); the national goal is 100% of hospitals by 2020.

*More information on CDC’s Core Elements of Hospital Antibiotic Stewardship Programs can be found at: https://www.cdc.gov/antibiotic-use/community/images/materials/2017-Core-Elements-Percentages.jpg

Source: CDC's National Healthcare Safety Network (NHSN) Survey
Community Antibiotic Prescriptions per 1,000 Population by State - 2016

Each year 270.2 million antibiotic prescriptions are written in the United States; equivalent to 836 antibiotic prescriptions per 1,000 persons.

Data source: IQVIA Xponent 2016

CDC’s Core Elements

CDC’s Core Elements of Antibiotic Stewardship for Hospitals, Nursing Homes, and Outpatient Settings

2014 Hospitals

2015 Nursing Homes

2016 Outpatient

2017 Small & Critical Access Hospitals
Clinician Checklist

[Image of the checklist]

https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_check_2_508.pdf
National Timeline for Implementing Antimicrobial Stewardship Programs

- President Obama issues Executive Order 13676 to combat antibiotic-resistant bacteria.
- CMS releases proposed CoP requiring antimicrobial stewardship.
- The Joint Commission begins surveying hospitals for compliance with antimicrobial stewardship standards.
- All healthcare delivery systems will demonstrate antimicrobial stewardship.

**September 2014**
- The National Action Plan to Combat Antibiotic-Resistant Bacteria is published.

**March 2015**
- ASPs, antimicrobial stewardship programs; CMS, Centers for Medicare & Medicaid Services

**June 2016**
- The Joint Commission releases requirements for ASPs.

**January 2017**
- **2018**
- All healthcare delivery systems will demonstrate antimicrobial stewardship.

**December 2019**
- The Joint Commission proposed new requirements for antimicrobial stewardship in ambulatory healthcare setting.

The Joint Commission’s Elements of Performance

Proposed new requirements for antimicrobial stewardship in the ambulatory healthcare setting

The organization:

1. **Identifies an individual(s)** responsible for developing, implementing, and monitoring activities to promote appropriate antimicrobial medication prescribing practices

2. Sets at least **one annual antimicrobial stewardship goal**

3. **Uses approved protocols and evidence-based practice guidelines** related to its annual antimicrobial stewardship goal(s)

https://www.jointcommission.org/antimicrobial_stewardship_%E2%80%93_ambulatory_health_care_ahc/
4. Provides staff and practitioners with educational resources related to its antimicrobial stewardship goal(s) and strategies that promote appropriate antimicrobial medication prescribing practices.

5. When the patient’s care, treatment, or services are related to an annual antimicrobial stewardship goal, the organization educates the patient, and the family as needed about appropriate prescribing of antimicrobial medications, potential adverse drug events from antimicrobial medications, importance of treatment adherence, and symptom management and duration.

6. Collects, analyzes, and reports data pertaining to the antimicrobial stewardship goal(s) to organizational leadership.

https://www.jointcommission.org/antimicrobial_stewardship_%E2%80%93_ambulatory_health_care_ahc/
Audience Question

The Core Elements of Outpatient Antibiotic Stewardship are:

A) Pledge, Action for Policy and Practice, Tracking and Reporting, Education and Expertise.

B) Action for Policy and Practice, Tracking and Reporting, Education and Dedication.

C) Dedication, Action for Policy and Practice, Tracking and Reporting, Education and Expertise.

Commitment, Action for Policy and Practice, Tracking and Reporting, Education and Expertise.
What Methods are Effective in Promoting Antimicrobial Stewardship?

• Prior authorization of antimicrobials/formulary restriction*
• Antimicrobial audit and feedback*

* Strong recommendation based on moderate quality evidence to use
Prior Authorization/Formulary Restriction

Provider writes order for “restricted drug”

Order arrives in pharmacy; pharmacist informs provider that drug is “restricted”/“not part of the pathway”/“nonformulary”

Prescribing provider and the “GATE KEEPER” converse

Approval or alternative antibiotic selected
Prospective Audit and Feedback

Provider writes order

Antibiotic is dispensed

1) Antibiotic change/continued based on Practice Guidelines

2) Prescribing provider contacted and recommendation made

At a later date, antibiotics are reviewed

(Targeted list, culture data, mismatches, ICU patients, duration)
Other Initiatives

- Antibiotic Awareness Week
  - WHO
  - CDC
  - https://www.cdc.gov/antibiotic-use/week/index.html

*Studies show that in otherwise healthy children and adults, antibiotics for bronchitis won't help you feel better.*
DISCUSS NOVEL AGENTS RECENTLY APPROVED WITH ACTIVITY AGAINST AR ORGANISMS
Novel Agents

• AR is inevitable
• Innovative strategies are needed to identify new antibiotics and develop treatment methods that are less likely to result in resistance
• U.S. National Strategy for Combating Antibiotic-Resistant Bacteria
• Infectious Disease Society of America (IDSA): The 10 x ‘20 Initiative
  • 10 new systemic antibacterial drugs by 2020
  • Discovery of new drug classes
  • New drugs from existing classes
Ceftolozane/tazobactam (Zerbaxa®)

Advanced-generation cephalosporin with beta-lactamase inhibitor

<table>
<thead>
<tr>
<th>FDA approved</th>
<th>December 19, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications (Adults)</strong></td>
<td></td>
</tr>
<tr>
<td>• Complicated intra-abdominal infections (cIAI)</td>
<td></td>
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<tr>
<td>• Complicated urinary tract infections, including pyelonephritis (cUTI)</td>
<td></td>
</tr>
<tr>
<td><strong>Spectrum of Activity</strong></td>
<td></td>
</tr>
<tr>
<td>• <em>Enterobacter cloacae</em>, <em>Escherichia coli</em>, <em>Klebsiella oxytoca</em>, <em>Klebsiella pneumoniae</em>, <em>Proteus mirabilis</em>, <em>Pseudomonas aeruginosa</em>, <em>Bacteroides fragilis</em></td>
<td></td>
</tr>
<tr>
<td>• <strong>Limited activity against anaerobes</strong> (except <em>B. fragilis</em>)</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td></td>
</tr>
<tr>
<td>cIAI: IV: 1.5 g every 8 hours for 4 to 14 days in combination with metronidazole</td>
<td></td>
</tr>
<tr>
<td>cUTI: IV: 1.5 g every 8 hours for 7 days</td>
<td></td>
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<tr>
<td><strong>Common Side Effects</strong></td>
<td>Nausea, diarrhea, headache</td>
</tr>
</tbody>
</table>
### Ceftazidime/avibactam (Avycaz®)

**Advanced-generation cephalosporin with non-beta-lactam beta-lactamase inhibitor**

<table>
<thead>
<tr>
<th><strong>FDA approved</strong></th>
<th>February 25, 2015</th>
</tr>
</thead>
</table>
| **Indications (Adults)** | • cIAI  
  • cUTI  
  • Pneumonia, hospital-acquired and ventilator-associated (HAP/VAP) |
| **Spectrum of Activity** | • *Citrobacter freundii* complex, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *Serratia marcescens*, *Haemophilus influenzae*  
  • **Limited activity against anaerobes** |
| **Dosing** |  
  **cIAI**: IV: 2.5 g every 8 hours in combination with metronidazole for 5 to 14 days  
  **HAP/VAP**: IV: 2.5 g every 8 hours for 7 to 14 days  
  **cUTI**: IV: 2.5 g every 8 hours for 7 to 14 days |
| **Common Side Effects** | Seizures (particularly with renal failure), nausea, vomiting, anxiety, diarrhea |

# Delafloxacin (Baxdela®)

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
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<tr>
<td>Indications (Adults)</td>
<td>SSTI</td>
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<tr>
<td>Spectrum of Activity</td>
<td>• Methicillin-susceptible (MSSA) and –resistant <em>Staphylococcus aureus</em> (MRSA), <em>streptococci</em> spp., • <em>E. coli, E. cloacae, K. pneumoniae</em>, and <em>P. aeruginosa</em> (less than ciprofloxacin) • <em>Peptostreptococcus</em> spp. and <em>B. fragilis</em> • Atypical pathogens</td>
</tr>
<tr>
<td>Dosing</td>
<td>Oral: 450 mg every 12 hours for 5 to 14 days IV: 300 mg every 12 hours for 5 to 14 days</td>
</tr>
<tr>
<td>Common Side Effects</td>
<td>Nausea, diarrhea, tendonitis, arthralgia, confusion May lower absorption of delafloxacin (chelation): antacids, iron, zinc</td>
</tr>
</tbody>
</table>

# Meropenem/vaborbactam (Vabomere®)

<table>
<thead>
<tr>
<th>Carbapenem Beta-Lactamase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approved</strong></td>
</tr>
<tr>
<td><strong>Indications (Adults)</strong></td>
</tr>
</tbody>
</table>
| **Spectrum of Activity**            | • *E. coli, K. pneumoniae, and E. cloacae*  
|                                     | • Activity against *K. pneumoniae* carbapenemase (KPC) producing *E. coli* and *K. pneumoniae*  
|                                     | • Gram (+) and Gram (-) aerobic (including *P. aeruginosa*) and anaerobic bacteria |
| **Dosing**                          | IV: 4 g every 8 hours for ≤14 days |
| **Common Side Effects**             | • Seizure potential, thrombocytopenia, phlebitis, diarrhea, headache  
|                                     | • Risk for breakthrough seizures due to drug interaction with valproic acid |

# Omadacycline (Nuzyra®)

<table>
<thead>
<tr>
<th>Tetracycline</th>
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</thead>
<tbody>
<tr>
<td><strong>FDA approved</strong></td>
</tr>
</tbody>
</table>
| **Indications (Adults)** | • Community-acquired pneumonia (CAP)  
• Skin and soft tissue infections (SSTI) |
| **Spectrum of Activity** | • **MSSA, MRSA, Streptococci spp.**  
• **Enterobacteriaceae, H. influenza, Acinetobacter baumannii, and Stenotrophomonas maltophilia**  
• Atypical pathogens  
• **Lacks Pseudomonas spp coverage** |
| **Dosing (CAP)** | Loading dose: IV: 200 mg as a single dose on day 1 or 100 mg twice daily on day 1  
Maintenance dose:  
• IV: 100 mg once daily  
• Oral: 300 mg once daily  
Duration of therapy: 7 to 14 days |
| **Dosing (SSTI)** | Loading dose:  
• IV: same as above  
• Oral: 450 mg once daily on days 1 and 2  
Maintenance dose: same as above  
Duration of therapy: same as above |
| **Common Side Effects** | Transaminitis, hypertension, insomnia, and gastrointestinal upset |

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Pharmacotherapy. 2019;39(2):207  
Zoliflodacin

<table>
<thead>
<tr>
<th>Class unknown (inhibits DNA synthesis)</th>
</tr>
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<tbody>
<tr>
<td>FDA approved</td>
</tr>
<tr>
<td>Indications (Adults)</td>
</tr>
<tr>
<td>Spectrum of Activity</td>
</tr>
<tr>
<td>Dosing</td>
</tr>
<tr>
<td>Common Side Effects</td>
</tr>
</tbody>
</table>

**Taylor et al.**
- 179 individuals with possible and/or confirmed exposure to gonorrhea
- Zoliflodacin PO (2 or 3 g) x 1 or ceftriaxone 500 mg IM x 1
- 98% (2 g zoliflodacin), 100% (3 g zoliflodacin), and 100% (ceftriaxone) were considered cured of their urogenital gonorrhea based on culture results
- Zoliflodacin cured all rectal gonorrheal infections as did ceftriaxone
- Did not fare as well in treating patients with gonorrhea infections of the throat (pharyngeal)
Audience Matching

- Omadacyline
- Delafloxacin
- Ceftolozane/tazobactam
- Zoliflodacin
- Meropenem/vaborbactam
- Ceftazidime/avibactam
- Risk for breakthrough seizures due to drug interaction with valproic acid
- 1st FQ with activity against MRSA
- Loading doses are required at therapy initiation
- FDA approved for uncomplicated urogenital Gonorrhea
- Better activity against K. pneumoniae carbapenemase (KPC) producing E. coli and K. pneumoniae compared to P. aeruginosa
- Has potent activity against many isolates of pseudomonas aeruginosa
Conclusions

• Numerous factors are associated with AR, but the most important and modifiable is the over-use of antibiotics.
• The current epidemiology of clinically important AR organisms highlights the continued need for improved strategies and novel agents directed at this problem.
• Antibiotic stewardship is an important strategy to combat antibiotic resistance, improve patient safety, and deliver high-quality healthcare.
• Approaches to optimize the use of both existing and newly developed antibiotics are of critical importance to ensure the best care to patients.
Questions