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 etc.
  - Focus shift: 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

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

1940 1960 1980

US Infection Death Rate per 100,000 population

200

100

Sulfa
Penicillin

Armstrong GL et al. JAMA 1999;281:61-66
Spellberg B. Rising Plague. Amherst, N.Y.: Prometheus Books, 2009
## Impact on Infectious Disease Related Mortality

<table>
<thead>
<tr>
<th>Disease</th>
<th>Death: Pre-Antibiotics</th>
<th>Death: Post-Antibiotics</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>~ 35%</td>
<td>~ 10%</td>
<td>- 25%</td>
</tr>
<tr>
<td>HAP</td>
<td>~ 60%</td>
<td>~ 30%</td>
<td>- 30%</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>~ 100%</td>
<td>~ 25%</td>
<td>- 75%</td>
</tr>
<tr>
<td>CNS Infection</td>
<td>&gt; 80%</td>
<td>&lt; 20%</td>
<td>- 60%</td>
</tr>
<tr>
<td>Skin Infection</td>
<td>11%</td>
<td>&lt; 0.5%</td>
<td>- 10%</td>
</tr>
<tr>
<td>Treatment of MI: aspirin &amp; clot busting drugs</td>
<td>- 3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAP = community acquired pneumonia, HAP = hospital acquired pneumonia, CNS = central nervous system, MI = myocardial infarction
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

Spellberg B. Rising Plague. Amherst, N.Y.: Prometheus Books, 2009
The Dark Ages
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
Foreshadowing

“…the microbes are educated to resist penicillin and a host of penicillin-fast (resistant) organisms is 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 this evil can be averted.”

- Sir Alexander Fleming, 1945
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
Resistence 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
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

Albrich WC et al. Emerg infect Dis 2004;10:514
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.
Inpatients <= 18 Yrs old; excludes normal newborns, Ob/Gyn, & Pav; includes mortalities

Chart from PHIS Antibiotic Stewardship Report V2.
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
Antibiotic Production

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Antibiotic</th>
<th>Year of Approval or Introduction to Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta)-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>

![Graph showing years from approval or introduction to market to first clinical report of resistance](image)
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

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Marston H et al. JAMA. 2016;316(11):1193-1204
CDC Antibiotic resistance threats in the United States, 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><strong>Carbapenem resistant Enterobacteriaceae (CRE)</strong></td>
<td>Extended spectrum beta-lactamase (ESBL) producing <em>Enterobacteriaceae</em></td>
<td>Erythromycin resistant Group A <em>Streptococcus</em></td>
</tr>
<tr>
<td>Drug-resistant <em>Neisseria gonorrhoea</em></td>
<td>Vancomycin resistant <em>Enterococcus</em></td>
<td>Clindamycin resistant Group B <em>Streptococcus</em></td>
</tr>
<tr>
<td></td>
<td><strong>MDR Pseudomonas</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methicillin resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug resistant <em>Streptococcus pneumoniae</em></td>
<td></td>
</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

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

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

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

- 11 countries in Asia (2004)
  - 685 isolates: 52% penicillin (I) or (R)

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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
    - Increasing pediatric incidence
  - Most isolates are sensitive to other (not beta-lactam) antibiotics
    - pUSA03 plasmid – fluoroquinolone, tetracycline, and clindamycin resistance

**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
  - Cohort of CAUTI, VAP, and catheter-related bloodstream infections:
    - 22-26 % for extended-spectrum cephalosporins
    - 16-19% for piperacillin tazobactam
    - 30-33% for fluoroquinolones
    - 24-28% for carbapenems
    - 17-23 % for aminoglycosides

- Approximately 20% of all isolates were MDR
  - Limited treatment options and/or use of agents with severe toxicity potential
**N. gonorrhoeae**

- Gram negative coccus occurring in pairs (diplococci)
  - Sexually transmitted
  - Congenital

- 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 250,000 infections per year
  - Rapid increase in AR in the USA, but especially globally

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**

- **2010**: CDC - dual therapy for treatment
- **2012**: CDC - ceftriaxone + azithromycin or doxycycline (only 1\textsuperscript{st} line)
- **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
    - General and reproductive health consequences

Carbapenem Resistant *Enterobacteriaceae* (CRE)

- **Enterobacteriaceae**
  - *Escherichia, Klebsiella, Citrobacter, Enterobacter* etc.
  - Variety of healthcare associated infections

- **Carbapenems (extremely broad spectrum)**
  - **NOT covered**: MRSA, *Stenotrophomonas, Enterococcus* spp., atypicals
  - **Common uses**: Infections due to ESBL and other MDR organisms

- **CRE**
  - 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 %

### Graph

- **Pt w/ CRKP**
  - Overall Mortality: OR 3.71 [95% CI 1.97-7.01]
  - Attributable Mortality: OR 4.50 [95% CI 2.16-9.35]

- **Pt w/ CSKP**
  - Overall Mortality: 20
  - Attributable Mortality: 12

**CRKP** = carbapenem resistant *Klebsiella pneumoniae*
**CSKP** = carbapenem susceptible *Klebsiella pneumoniae*
CRE: *K. pneumoniae* Carbapenemase (KPC)
CRE: K. pneumoniae Carbapenemase (KPC)
Local CRE Incidence

Texas Children's Hospital:
Total Number of Isolates by Year

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>8</td>
<td>16</td>
</tr>
</tbody>
</table>

% of Carbapenem Resistant Isolates from 2011 - 2016

- **E. coli** isolates have more than doubled in the last year
- 2% increase per year in **K. pneumoniae** isolates
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
- White House Forum on Antibiotic Stewardship
- U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria
- 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 examined the effect of implementation of a hospital-based stewardship program on *E. coli* antibiotic resistance between 2008 and 2014

• Two academic hospitals – one with an antibiotic stewardship program and one control hospital without a program

• 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 was also observed in the experimental group
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.
- 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 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 (3,816 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 of Antibiotic Stewardship for Hospitals, Nursing Homes, and Outpatient Settings

2014 Hospitals
2015 Nursing Homes
2016 Outpatient
2017 Small & Critical Access Hospitals
**Clinician Checklist**

**COMMITMENT**

1. Can you demonstrate dedication to and accountability for optimizing antibiotic prescribing and patient safety related to antibiotics?  
   If yes, indicate which of the following are in place (select all that apply)
   - Write and display public commitments in support of antibiotic stewardship.

**ACTION**

2. Have you implemented at least one practice to improve antibiotic prescribing?  
   If yes, indicate which practices which you use. (Select all that apply.)
   - Use evidence-based diagnostic criteria and treatment recommendations.
   - Use delayed prescribing practices or watchful waiting, when appropriate.

**TRACKING AND REPORTING**

3. Do you monitor at least one aspect of antibiotic prescribing?  
   If yes, indicate which of the following are being tracked. (Select all that apply.)
   - Self-evaluate antibiotic prescribing practices.
   - Participate in continuing medical education and quality improvement activities to track and improve antibiotic prescribing.

**EDUCATION AND EXPERTISE**

4. Do you provide education to patients and seek out continuing education on antibiotic prescribing?  
   If yes, indicate how you provide antibiotic stewardship education. (Select all that apply)
   - Use effective communications strategies to educate patients about when antibiotics are and are not needed.
   - Educate about the potential harms of antibiotic treatment.
   - Provide patient education materials.
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.

- MARCH 2015
- JUNE 2016
- JANUARY 2017
- 2018
- 2020

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/
Elements of Performance continued…

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/
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

1) Antibiotic change/continued based on Practice Guidelines

2) Prescribing provider contacted and recommendation made

Antibiotic is dispensed

At a later date, antibiotics are reviewed

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

- Antibiotic Awareness Week

https://www.cdc.gov/antibiotic-use/week/index.html
Other Initiatives

• Immunizations
• Removal of temporary medical devices
• Hand hygiene
• Contact precautions
DISCUSS NOVEL AGENTS RECENTLY APPROVED WITH ACTIVITY AGAINST AR ORGANISMS
Novel Agents

• AMR to antibiotics is inevitable
• Innovative strategies are needed to identify new antibiotics and develop treatment methods that are less likely to result in resistance
Novel Agents

- 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®)

<table>
<thead>
<tr>
<th>Advanced-generation cephalosporin with beta-lactamase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approved</strong></td>
</tr>
<tr>
<td><strong>Indications (Adults)</strong></td>
</tr>
<tr>
<td>• Complicated intra-abdominal infections (cIAI)</td>
</tr>
<tr>
<td>• Complicated urinary tract infections, including pyelonephritis (cUTI)</td>
</tr>
<tr>
<td>• Ventilator-associated nosocomial pneumonia: clinical trial in progress</td>
</tr>
<tr>
<td><strong>Spectrum of Activity</strong></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>
</tr>
<tr>
<td>• <strong>Limited activity against anaerobes</strong> (except <em>B. fragilis</em>)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td><strong>cIAI</strong>: IV: 1.5 g every 8 hours for 4 to 14 days in combination with metronidazole</td>
</tr>
<tr>
<td><strong>cUTI</strong>: IV: 1.5 g every 8 hours for 7 days</td>
</tr>
<tr>
<td><strong>Common Side Effects</strong></td>
</tr>
</tbody>
</table>
### Ceftazidime/avibactam (Avycaz®)

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

<table>
<thead>
<tr>
<th>FDA approved</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><strong>Fluoroquinolone</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA approved</strong></td>
</tr>
<tr>
<td><strong>Indications (Adults)</strong></td>
</tr>
<tr>
<td><strong>Spectrum of Activity</strong></td>
</tr>
<tr>
<td>• Methicillin-susceptible (MSSA) and –resistant <em>Staphylococcus aureus</em> (MRSA), <em>streptococci spp.</em>,</td>
</tr>
<tr>
<td>• <em>E. coli, E. cloacae, K. pneumoniae</em>, and <em>P. aeruginosa</em> (less than ciprofloxacin)</td>
</tr>
<tr>
<td>• <em>Peptostreptococcus spp.</em> and <em>B. fragilis</em></td>
</tr>
<tr>
<td>• Atypical pathogens</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>Oral: 450 mg every 12 hours for 5 to 14 days</td>
</tr>
<tr>
<td>IV: 300 mg every 12 hours for 5 to 14 days</td>
</tr>
<tr>
<td><strong>Common Side Effects</strong></td>
</tr>
<tr>
<td>Nausea, diarrhea, tendonitis, arthralgia, confusion</td>
</tr>
<tr>
<td>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>FDA approved</td>
</tr>
<tr>
<td>Indications (Adults)</td>
</tr>
<tr>
<td>Spectrum of Activity</td>
</tr>
<tr>
<td>• <em>E. coli</em>, <em>K. pneumoniae</em>, and <em>E. cloacae</em></td>
</tr>
<tr>
<td>• Activity against <em>K. pneumoniae</em> carbapenemase (KPC) producing <em>E. coli</em> and <em>K. pneumoniae</em></td>
</tr>
<tr>
<td>• Gram (+) and Gram (-) aerobic and anaerobic bacteria</td>
</tr>
<tr>
<td>Dosing</td>
</tr>
<tr>
<td>Common Side Effects</td>
</tr>
<tr>
<td>• Seizure potential, thrombocytopenia, phlebitis, diarrhea, headache</td>
</tr>
<tr>
<td>• Risk for breakthrough seizures due to drug interaction with valproic acid</td>
</tr>
</tbody>
</table>
# Omadacycline (Nuzyra®)

<table>
<thead>
<tr>
<th>Tetracycline</th>
</tr>
</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 |
Zoliflodacin

Class unknown (inhibits DNA synthesis)

<table>
<thead>
<tr>
<th>FDA approved</th>
<th>Pending (will begin Phase 3 test this coming year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications (Adults)</td>
<td>Uncomplicated urogenital Gonorrhea</td>
</tr>
<tr>
<td>Spectrum of Activity</td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td>Dosing</td>
<td>Oral: 2g or 3g once</td>
</tr>
<tr>
<td>Common Side Effects</td>
<td>Transient gastrointestinal upset</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)
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