Resistance is Futile
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NEFSP Presentation
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Objectives
- Describe the Generating Antibiotic Incentives Now (GAIN) Act
- Identify new antimicrobial therapies approved by the Food and Drug Administration (FDA)
- Discuss the mechanism of action, side effects, and place in therapy of antimicrobials approved by the FDA

Disclosure Statement
I have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation.

History of Antimicrobial Development
- Decrease in antimicrobial development
  - 2014-2015: 6 antimicrobials
- Factors in development
  - Production cost
  - Drug discovery shift
  - Novel mechanism
  - Controlling resistance

Bad Bugs, No Drugs
- Bad bugs, no drugs report 2004
  - 2010 report
    - Target ESKAPE
    - 10 x 20 Initiative
      - Initiated IDSA in 2010
      - Promotes research and development
    - Revision to Food and Drug Administration Safety and Innovation Act of 2012

Generating Antibiotic Incentives Now (GAIN) Act
- Bill introduced in June 2011; passed in July 2012
- Purpose to promote development of antibacterial and antifungal drugs
  - Response to increasing organism resistance
  - Serious or life threatening infection

4. http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/ucm218116.htm
Defining Qualifying Pathogens

- Certain qualified pathogens
- FDA lists 4 criteria to be a qualified pathogen\(^1,2\)
  - Impact on public health
  - Growth of drug resistant organisms
  - Increase in resistance rates
  - Morbidity and mortality
- Qualified pathogens → Qualified Infectious Disease Product (QIDP)

Generating Antibiotic Incentives Now (GAIN) Act

- Requires FDA to review clinical trial guidelines
  - Recommendations by IDSA
  - Consult with infectious disease and resistance experts
- Financial incentives
  - Expedited review by FDA
  - Market exclusivity for 5 additional years
  - Additional 6 months for a companion diagnostic test

Antibiotic Timeline

Dalbavancin (Dalvance®)
Oritavancin (Orbactiv®)
Indazolid (Sivextro®)
Ceftolozane-tazobactam (Zerbaxa®)
Tedizolid (Sivextro®)
Ceftolozane-tazobactam: Spectrum of Activity

- MoA: Inhibits cell wall synthesis and binds to penicillin binding proteins (PBPs)\(^1\)
  - Bactericidal activity; time/MIC parameter
- Indications\(^1,2\)
  - Complicated urinary tract infections (cUTI) including pyelonephritis
  - Complicated intra-abdominal infections (cIAI) with metronidazole
  - Pending use for nosocomial pneumonia (phase III)

Ceftolozane-Tazobactam: Brand name: Zerbaxa®
- Cephalosporin/beta lactamase inhibitor combination
  - Complex side chains overcome resistant mechanisms of P. aeruginosa
  - Beta lactamase inhibitor prevents hydrolysis of ceftolozane

2. FDA. The Federal Register. 79 FR 32464–32481.

Ceftolozane-Tazobactam: Recommended Dosing
- 1 g ceftolozane/0.5 g tazobactam IV q8hr
- Infusion time 1 hr
- Pneumonia dose: 2 g ceftolozane/1 g tazobactam IV q8hr
- Label confusion
- Renal adjustment when creatinine clearance (CrCl) < 50 mL/min

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 50 mL/min</td>
<td>800 mg/250 mg IV q8hr</td>
</tr>
<tr>
<td>15 to 29 mL/min</td>
<td>250 mg/125 mg IV q8hr</td>
</tr>
<tr>
<td>&lt; 15 mL/min</td>
<td>No recommendation</td>
</tr>
<tr>
<td>ESRD</td>
<td>Single loading dose of 500 mg/250 mg IV; 100 mg/50 mg q8hr IV</td>
</tr>
</tbody>
</table>

*Using Cockcroft-Gault formula

3. "Ceftolozane-Tazobactam (Zerbaxa) (package insert)."

Ceftazidime-Avibactam
- Brand name: Avycaz®
- 3rd generation cephalosporin/ beta lactamase inhibitor
- MoA: Inhibits cell wall synthesis and binds to PBPs
- Bactericidal activity: time/MIC parameter
- Indications
  - cUTI including pyelonephritis
  - cIAI
  - Pending use nosocomial pneumonia (phase III)

3. Ceftazidime-avibactam (Avycaz) [package insert]

Ceftazidime-Avibactam: Spectrum of Activity
- Gram negative coverage
  - Avibactam enhances coverage to AmpC, CRE, and ESBL
  - Ambler classification system
  - Classes A, C, and D
  - Enterobacteriaceae
    - Klebsiella species
    - E. coli
    - MDR P. aeruginosa
    - Citrobacter species
    - Enterobacter species


Ceftolozane-Tazobactam
- Adverse effects
  - Nausea (5.2%)
  - Diarrhea (3.9%)
  - Headache (4.2%)
  - Pyrexia (3.3%)
- Monitoring
  - Renal function
  - Cost
  - Wholesale acquisition cost (WAC) $83 per vial
  - WAC per day $25-$240

2. Ceftolozane-Tazobactam (Zerbaxa) [package insert].

Avibactam: The New Kid on the Block
- Novel non-beta lactam, beta lactamase inhibitor
- Acyl enzyme stabilizes beta lactamase and promotes recylation
- Combined with beta lactam to extend spectrum of activity


Ceftazidime-Avibactam: Spectrum of Activity
- Gram positive
  - Staphylococcus species
- Limited Staphylococcus
- Ceftazidime-avibactam not fully assessed
- Anaerobes
  - B. fragilis
  - C. perfringens
  - Prevotella species


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- Anaerobes
  - B. fragilis
  - C. perfringens
  - Prevotella species

Ceftazidime-Avibactam: Recommended Dosing
- 2 g ceftazidime/0.5 g IV avibactam
- Infusion time 2 hr
- Renal dose adjustment required

<table>
<thead>
<tr>
<th>Creatinine clearance*</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 to 50 mL/min</td>
<td>1.0 g/0.25 g IV q8hr</td>
</tr>
<tr>
<td>16 to 30 mL/min</td>
<td>0.75 g/0.19 g IV q12hr</td>
</tr>
<tr>
<td>6 to 15 mL/min</td>
<td>0.75 g/0.19 g IV q24hr</td>
</tr>
<tr>
<td>≤ 5 mL/min</td>
<td>0.75 g/0.19 g IV q48hr</td>
</tr>
</tbody>
</table>

*Using Cockcroft-Gault formula

Ceftazidime-Avibactam

- Adverse effects (≥ 10%)
  - Vomiting
  - Nausea
  - Constipation
  - Anxiety
  - Monitoring
  - Renal function
  - Cost
  - WAC $285 per vial

Tedizolid: The New Ox on the Block
- Brand name: Sivextro®
- Oxazolidinone drug class
- Prodrug: tedizolid phosphate to tedizolid
- MoA: Inhibits bacterial protein synthesis
- Bacteriostatic activity: AUC/MIC parameter
- Overcomes chloramphenicol-florfenicol resistance (cfr) resistance mechanism
- Indications
  - Acute bacterial skin and skin structure infections (ABSSSI)
  - Pending approval for nosocomial pneumonia
- Dosing
  - 200 mg PO or IV q24hr for 6 days
  - 1:1 conversion for IV to PO

Tedizolid: Spectrum of Activity
- Overcomes chloramphenicol-florfenicol resistance (cfr) resistance mechanism

Tedizolid Medication Safety
- Adverse effects
  - Nausea (8%)
  - Headache (6%)
  - Diarrhea (4%)
  - Thrombocytopenia (2%)
  - Incidence less in tedizolid 2.1% vs linezolid 4.5% (p=0.0175)
- Monitoring
- CBC

References:
1. Ceftazidime-Avibactam (Avycaz) [package insert]
2. “Arceus Approval and Labeling Restrictions.”
3. Tedizolid [Generic] (Sivextro) [package insert]
<table>
<thead>
<tr>
<th>Tedizolid¹</th>
<th>Linezolid²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>ABSSSI</td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td>MSSA</td>
</tr>
<tr>
<td><strong>Enterococcus species (VRE)</strong></td>
<td>MRSA</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>Potent concentrations</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>200 mg IV/PO for 6 days</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>GI upset</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Minimal MAO inhibitor</td>
</tr>
<tr>
<td><strong>No serotonergic agents</strong></td>
<td>Serotonergic agents</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$386.67 per tablet</td>
</tr>
</tbody>
</table>

¹ Tedizolid (Sivextro) [package insert]
² Linezolid (Zyvox) [package insert]
³ Linezolid (Zyvox) Lexicomp Online. Isavuconazonium Sulfate

- **Brand name:** Cresemba®
- **Azole antifungal**
- **Prodrug that converts to active form isavuconazole¹**
- **MoA:** Inhibits the enzyme lanosterol 14-alpha-demethylase reducing production of ergosterol¹
- **Indications¹,²,³**
  - Invasive aspergillosis
  - Invasive mucormycosis

### Isavuconazonium: Spectrum of Activity

- Mold and yeast¹
  - Aspergillus fumigatus
  - Aspergillus niger
  - Mucorales (Rhizopus oryzae and mucormycetes species)

¹ Isavuconazonium sulfate (Cresemba®) [package insert].
² http://www.rxlist.com/cresemba-drug.htm

### Isavuconazonium: Dosage Forms and Dosing

- **Capsule**
  - 186 mg 2 caps PO q8hr for 6 doses
  - 186 mg 2 caps PO q24hr
  - 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole
- **Injection**
  - LD: 372 mg IV q8hr for 6 doses
  - MD: 372 mg IV q24hr
  - 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole

### Isavuconazonium: Medication Safety

- No renal impairment adjustments
- No mild or moderate hepatic adjustments; unknown with severe hepatic impairment
- Contraindications
  - Strong CYP3A4 inhibitors/inducers
  - Short QT syndrome
- Warnings/Precautions
  - Hepatic adverse reactions
  - Infusion related reactions

### Isavuconazonium Sulfate

- **Adverse effects (≥ 5%)³**
  - Nausea/vomiting/diarrhea
  - Hypokalemia
  - Cough
  - Peripheral edema
  - Back pain
- **Monitoring¹**
  - Liver function
  - Infusion reactions
- **Cost**
  - AWP $84 per capsule
  - AWP $286.20 per vial

¹ Isavuconazonium sulfate (Cresemba®) [package insert].
² NCT00413218.
Isavuconazonium Sulfate

- Pros
  - IV and PO options
  - Daily dosing for maintenance
  - Therapy for resistance or refractory patients
- Cons
  - Limited clinical trials (small sample size)
  - Drug interactions
- Place in therapy
  - Second to third line option

Summary

- GAIN Act promotes the creation of new antimicrobials that overcome MDRO
- Antimicrobials approved by the FDA provide clinical use in MDRO
- Recently approved antimicrobials have new mechanisms of actions, limited side effects, and distinct places in therapy

Assessment Question #1

Which of the following drug class(es) does the GAIN Act provide incentives and promote as a QIDP?

A. Antibacterials  
B. Antifungals  
C. Antivirals  
D. Anti-parasitics  
E. A and B only

Assessment Question #2

What feature describes ceftolozane-tazobactam mechanism of action allowing it to overcome resistant mechanisms of *P. aeruginosa*?

A. The beta lactamase inhibitor, tazobactam, is potent towards resistant mechanisms
B. The complex side chains of ceftolozane are able to neutralize resistant mechanisms
C. The large molecule size of ceftolozane diverts resistant mechanisms to tazobactam
D. The potent killing activity of ceftolozane-tazobactam overcomes resistant mechanisms

Assessment Question #3

What feature(s) is/are TRUE about avibactam?

A. Non-beta lactam, beta lactamase inhibitor
B. Recycling of the beta lactamase inhibitor allows repeated use to overcome resistance
C. Avibactam enhances coverage to AmpC, CRE, and ESBL infections
D. A and B only
E. All statements above are true

Resistance is Futile

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Meet the Vancins
- Dalbavancin (Dalcroine®)
  - Indication: ABSSSI
  - Dose: 1000 mg IV once; 500 mg IV 1 week later (over 30 min)
  - Microbiology: S. aureus (including MRSA), Streptococcus species, and Enterococcus species
  - Adverse effects: Nausea, headache, and diarrhea
- Oritavancin (Orbactiv®)
  - Indication: ABSSSI
  - Dose: 1200 mg IV single dose (infused 3 hr)
  - Microbiology: S. aureus (including MRSA), Streptococcus species, and Enterococcus species
  - Adverse effects: Nausea, vomiting, headache, and diarrhea

Ceftazidime-Avibactam: Spectrum of Activity

<table>
<thead>
<tr>
<th>Ambler Classification</th>
<th>Enzyme</th>
<th>Most Common Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>KPC, SME, IMI, NMC, GES</td>
<td>Enterobacteriaceae (ESBL and carbapenemases)</td>
</tr>
<tr>
<td>Class B (metallo-β-lactamase)</td>
<td>IMP, VIM, GIM, SPM</td>
<td>P. aeruginosa Enterobacteriaceae Acinetobacter spp.</td>
</tr>
<tr>
<td>Class C</td>
<td>AmpC, FOX, CMY, LAT, ACC, DHA</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Class D</td>
<td>OXA</td>
<td>Acinetobacter spp.</td>
</tr>
</tbody>
</table>

Ceftazidime-Avibactam MIC Values

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (μg/mL)</th>
<th>Disk Diffusion Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S  I  R</td>
<td>S  I  R</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>≥0.5  4  8</td>
<td>≥0.5  4  8</td>
</tr>
<tr>
<td>S. pneumonia</td>
<td>≥0.5  -  -</td>
<td>≥0.5  -  -</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>≥0.5  -  -</td>
<td>≥0.5  -  -</td>
</tr>
<tr>
<td>E. coli</td>
<td>≥0.5  -  -</td>
<td>≥0.5  -  -</td>
</tr>
</tbody>
</table>

References
References Continued


References Continued