New Antibiotics for the Post-Antibiotic Era

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Disclosures
• I have no conflicts of interest relative to the content of this presentation

Objectives for Pharmacists
• Review recently approved antimicrobials including their spectrum of activity and potential place in therapy
• Discuss the pertinent antimicrobial stewardship implications of newly approved agents
• Identify antimicrobial agents in the advanced stages of the drug development pipeline and assess their potential implications for infectious diseases pharmacotherapy

Objectives for Technicians
• Review recently approved antimicrobials including their spectrum of activity and potential place in therapy
• Discuss the pertinent antimicrobial stewardship implications of newly approved agents
• Identify antimicrobial agents in the advanced stages of the drug development pipeline.

220/146 mmHg
“We’re here. We’re in the post-antibiotic era. There are patients for whom we have no therapy, and we are literally in a position of having a patient in a bed who has an infection, something that five years ago even we could have treated, but now we can’t….”

- Arjun Srinivasan, MD
Associate Director for Healthcare Associated Infection Prevention Programs, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases

The Problem

• What % of Gram negative *Enterobacteriaceae* are ESBL + across the continental United States?
  • ~15%
• What % of Gram negative *Enterobacteriaceae* are ESBL + in the Illinois region?
  • ~15%

Meropenem Non-susceptible *K. pneumoniae*

Meropenem Non-susceptible *P. aeruginosa*
The Health-System Problem

- **Antibiogram**
- UIC resistance rates
  - ESBL
    - *E. coli* ~ 10%
    - *K. pneumoniae* ~ 15%
  - CRE ~ 9%
  - MDR *P. aeruginosa* ~ 20%

(Right) (Part of) The Solution

Antibiotic approvals

Recently approved antimicrobials

- Dalbavancin – May 2014
- Tedizolid – June 2014
- Oritavancin – August 2014
- Ceftolozane-tazobactam – December 2014
- Ceftazidime-avibactam – February 2015

Ceftolozane-tazobactam

- **Dalbavancin**
- **Tedizolid**
- **Oritavancin**
- **Ceftolozane-tazobactam**
- **Ceftazidime-avibactam**

Ceftolozane-tazobactam

- **Dalbavancin**
- **Tedizolid**
- **Oritavancin**
- **Ceftolozane-tazobactam**
- **Ceftazidime-avibactam**

Ceftolozane-tazobactam

- Primary *in vitro* activity is aerobic Gram negative bacilli
  - Poor Gram positive and anaerobe activity
    - Combine with metronidazole and/or Gram positive agent
  - Not reliable against *Acinetobacter* or *Stenotrophomonas* spp.
**Ceftolozane-tazobactam**
- Approved dose-1.5g Q8 hours\(^8\)-\(^{10}\)
- Adjusted for renal function
- Non-inferiority established in:
  - ASPECT cUTI: phase II+III cUTI\(^{11}\)
  - vs levofloxacin
  - ASPECT cIAI: phase II cIAI\(^{12}\), two phase III cIAI trials\(^{13}\)
  - vs meropenem
- Numerically lower cure rates in mild renal dysfunction
- AEs were mild and reversible

**Stewardship considerations**
- Primary place in therapy is MDR *Pseudomonas aeruginosa*
- Check local resistance rates
- Primary need is off-label for serious infections
- May decrease carbapenem use
- Existing resistance limits use
- Need susceptibility testing
- Extended infusion?

**Stewardship considerations**
- Likely need to restrict to prior authorization
- Cost:
  - 1.5g vial - $109.61
  - ~$2,300 for 7 day course
  - 3g dose being studied in VAP vs meropenem
- Needs to be given with metronidazole and/or Gram positive agent if used empirically
- Potential option for PCN allergies

**Ceftazidime-avibactam**
- Oxyimino cephalosporin
- Non-\(\beta\)-lactam \(\beta\)-lactamase inhibitor
- Inhibits class A, C, and D \(\beta\)-lactamases\(^{14}\)
- High threshold to resistance in *Enterobacteriaceae*\(^{15-21}\)
- Variable *P. aeruginosa* activity\(^{22-24}\)
- Limited Gram positive and anaerobic activity\(^{25}\)

**Ceftazidime-avibactam**

<table>
<thead>
<tr>
<th>(\beta)-Lactam</th>
<th>Avibactam</th>
<th>Ceftriaxone</th>
<th>Tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A (Serine)</td>
<td>TEM, SHV, and ESBLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CTX-M and ESBLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PER, VEB, GES</td>
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<tr>
<td></td>
<td>KPC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class B (Mimoty)</td>
<td>IMP, VIM, NDm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class C (Serine)</td>
<td>Chromoviolin Enterobacteriaceae AmpC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pseudomonas Amp</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluoroacil, ACC, DHA, FOX, LAT, MIX, MER, ACT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class D (Serine)</td>
<td>Variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variable</td>
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</tr>
</tbody>
</table>

\(^{26}\)
Ceftazidime-avibactam

- Approved dose is 2.5g Q8h
- Adjusted for renal function
- Non-inferiority established in:
  - 2 phase II cUTI trials
  - 1 phase II cIAI
  - RECLAIM 1+2: phase III cIAI trials

Ceftazidime-avibactam table

<table>
<thead>
<tr>
<th>Baseline Renal Function</th>
<th>Ceftazidime-avibactam</th>
<th>Meropenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 50 ml/min</td>
<td>292/374 (4%)</td>
<td>321/374 (80%)</td>
</tr>
<tr>
<td>CrCl 30 to &lt; 50 ml/min</td>
<td>143/374 (45%)</td>
<td>26/374 (74%)</td>
</tr>
</tbody>
</table>

Ceftazidime-avibactam 26

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Proposed Dosing Regimen</th>
<th>Ceftazidime (mg/L)</th>
<th>Avibactam (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normol with 50</td>
<td>2.5 g IV every 8 hours</td>
<td>45.6/131.4</td>
<td>542.1/163.1</td>
</tr>
<tr>
<td>MOD</td>
<td>2.5 g IV every 8 hours</td>
<td>38.9/123.1</td>
<td>514.5/160.1</td>
</tr>
<tr>
<td>Normol with 15</td>
<td>2.5 g IV every 8 hours</td>
<td>32.8/108.7</td>
<td>433.1/146.3</td>
</tr>
<tr>
<td>MOD</td>
<td>2.5 g IV every 8 hours</td>
<td>28.7/94.8</td>
<td>402.9/133.6</td>
</tr>
</tbody>
</table>

RECAPTURE 1 and 2

- Ceftazidime-avibactam 2.5g Q8h vs. doripenem 500mg Q8h for cUTI and AP
- Possible switch to PO after 5 days
- 1033 patients
- Primary endpoints:
  - Patient reported symptomatic resolution at day 5
  - Combined symptomatic resolution and microbiological eradication at TOC
**RECAPTURE 1 and 2**

- Non-inferiority was achieved
- Superiority with ceftazidime-avibactam in micro eradication at TOC
- No reduction in efficacy in renal impairment
- 1250 mg Q12h regimen was used for CrCl <50 mL/min
- No new safety concerns identified

**Ceftazidime-avibactam**

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Proposed Dosing Regimen</th>
<th>% of Simulated Patients Achieving PK/PD Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOM</td>
<td>2000 mg CAZ + 500 mg AVI, q8h</td>
<td>98.9</td>
</tr>
<tr>
<td>MILD</td>
<td>2000 mg CAZ + 500 mg AVI, q8h</td>
<td>99.9</td>
</tr>
<tr>
<td>MOD</td>
<td>1000 mg CAZ + 250 mg AVI, q12h</td>
<td>96.9</td>
</tr>
<tr>
<td>SEV1</td>
<td>1000 mg CAZ + 250 mg AVI, q12h</td>
<td>97.8</td>
</tr>
<tr>
<td>SEV2</td>
<td>500 mg CAZ + 125 mg AVI, q12h</td>
<td>100</td>
</tr>
<tr>
<td>ESRD</td>
<td>500 mg CAZ + 125 mg AVI, q12h</td>
<td>100</td>
</tr>
</tbody>
</table>

**REPRISE**

- Ceftazidime-avibactam 2.5g Q8h vs. best available therapy
- Patients with cUTI or cIAI d/t ceftazidime non-susceptible Gram negative pathogens
  - 97% received carbapenem
  - Pts with ongoing S&S could have received any treatment
  - Those who received effective therapy had to be clinically worsening
- Exclusion was CrCl <6 mL/min

**Stewardship considerations**

- Primary need is off-label for serious infections
- CRE is currently most urgent threat
  - Local resistance rates
  - *In vitro* activity, safety profile, and clinical experience with ceftazidime provide promise
  - Need additional clinical data for CRE
  - Allow for avoidance of polymyxins and aminoglycosides in CRE?
  - Combo therapy?
### Stewardship considerations
- Likely need to restrict to prior authorization
- Cost:
  - 2.5g vial - $359.10
  - $7,541.10 for 7 day course
- Needs to be given with metronidazole and/or Gram positive agent if used empirically
- Compatibility with vancomycin
- Drug not available until March

### Pipeline antimicrobials
- Currently in/completed phase III trials
  - Meropenem/vaborbactam
  - Eravacycline

### Meropenem-vaborbactam
- PK of vaborbactam shown to match meropenem extremely well
- ELF penetration 63% and 53%
- Currently in Phase III trials as fixed dose combination of 2g meropenem/2g vaborbactam Q8h as 3 hour infusion
- cUTI and AP vs piperacillin-tazobactam
- CRE infections vs. best available therapy

### Meropenem-vaborbactam
- cUTI and AP study completed June 2016
- Compared to piperacillin-tazobactam
  - Step-down to PO therapy
  - Met FDA and EMA non-inferiority endpoint
  - Superior to piperacillin-tazobactam in FDA endpoint
    - 188/192 (98.4%) vs. 171/182 (94%)
  - Microbiological eradication 66.7% vs. 57.7%
  - No unanticipated adverse events

### Other formulary concerns?

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Ceftolozane-Tazobactam</th>
<th>Ceftazidime-Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clinical trial data</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Safety</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cost</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Meropenem-vaborbactam

- Stewardship considerations
- Active against CREs
- When approved will have only clinical data in patients with CRE infections
- Will begin HAP/VAP trial soon vs. piperacillin-tazobactam
- Price?
- Susceptibility testing?

Eravacycline

- Novel, synthetic fluoroquinolone
- Active against ESBL, CRE, A. baumannii, MRSA, and VRE
- No P. aeruginosa activity
- Compared to tigecycline, improved:
  - PK
  - Tolerability
  - *in vitro* CRE activity

Eravacycline

- IGNITE 1
  - Phase III study vs ertapenem for cIAI
  - Met FDA and EMA primary endpoint of non-inferiority in clinical response at TOC in MITT group
  - 95% CI bounds -7.1%-5.5%
  - No serious adverse events
- IGNITE 2
  - Phase III trial in cUTI vs levofloxacin

Eravacycline

- IGNITE 2
  - 1.5 mg/kg daily followed by 200 mg PO Q12h vs levofloxacin 750 mg daily
  - Minimum of 3 IV days
  - Did not achieve either FDA or EMA non-inferiority endpoint
  - Not able to push dose to PO 400 mg due to adverse events
  - N/V similar to tigecycline

Eravacycline

- Stewardship considerations
- 1 mg/kg IV Q12h dose only going forward
  - PO dosage form?
  - Extremely broad activity
  - VRE and Acinetobacter spp.
  - Bacteriostatic
  - Tetracycline analogue
  - Pregnancy, pediatrics...

Summary

- Resistance among Gram negative pathogens will continue to increase
- Two new antimicrobials are promising although they do not address all relevant pathogens and clinical data in target infections are lacking
- Meropenem-vaborbactam should close some of the existing gaps in available agents
References


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Self-Assessment Questions

1. According to the 2013 Center for Disease Control and Prevention Antibiotic Resistance Threat Report, which of the following pathogens is categorized as a threat level of “urgent”?
   A. Multidrug-resistant *Pseudomonas aeruginosa*
   B. Extended spectrum β-lactamase producing (ESBL) *Enterobacteriaceae*
   C. Carbapenem-resistant *Enterobacteriaceae* (CRE)
   D. Vancomycin-resistant *Enterococcus* (VRE)

2. Resistant Gram negative pathogens are not a substantial problem in the Illinois region as local resistance rates are far less than national rates
   A. True
   B. False

3. Which of the following agents would be the most appropriate therapeutic option to treat a 67 year old patient with no known drug allergies and a CrCl of 52 mL/min with a complicated intra-abdominal infection (cIAI) due to carbapenem-resistant *K. pneumoniae*?
   A. Ceftazidime-avibactam 2.5g every 8 hours
   B. Meropenem 2g every 12 hours
   C. Ceftolozane-tazobactam 1.5g every 8 hours
   D. Fosfomycin 6g IV every 6 hours

4. Once FDA approved, which of the following agents will have the only in-human randomized controlled trial data to support its use for patients with serious infections due to carbapenem-resistant organisms?
   A. Eravacycline
   B. Ceftaroline-avibactam
   C. Delafloxacin
   D. Meropenem-vaborbactam

5. Which of the following agents has reliable activity against *Acinetobacter spp*?
   A. Meropenem-vaborbactam
   B. Ceftolozane-tazobactam
   C. Eravacycline
   D. Ceftazidime-avibactam
   E. None of the above

Answer key:

1. C
2. B
3. A
4. D
5. C