**Activity Description**

**Target Audience**
Addressing the challenges of MDR bacteria requires an interprofessional approach that includes all healthcare providers involved in the prevention, diagnosis, and management of patients with or at risk for these infections. Therefore, this continuing medical education activity targets a variety of healthcare providers that include ID physicians, infection control specialists, hospital epidemiologists, hospitalists, clinical microbiologists, nurses, and clinical pharmacists.

**Learning Objectives**
Upon completing this activity, participants will be able to:
- Discuss current epidemiological trends regarding multidrug-resistant (MDR) Gram-negative bacteria and their impact on clinical outcomes
- Summarize approaches aimed at minimizing the spread and development of antimicrobial resistance, including antimicrobial stewardship strategies and rapid diagnostic assays
- Evaluate the potential role of new and emerging antimicrobial agents as part of the treatment armamentarium when treating infections caused by MDR Gram-negative bacteria

**Faculty**

Keith A. Rodvold, PharmD, FCCP, FIDSA
Professor of Pharmacy Practice and Medicine
Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, IL

- In USA:
  - AMR organisms cause >2 million infections
  - 25,000 deaths each year (~25,000 in Europe)
  - Estimated $20 billion in excess medical spending each year
- Full global effect of AMR is difficult
- Recent global emergence:
  - USA (carbapenem-resistant Klebsiella pneumoniae)
  - India (bacteria with the plasmid-mediated blaNDM-1 gene that confers resistance to carbapenems)
  - Escherichia coli with plasmid-mediated mcr-1 gene that confers resistance to colistin (originally described in China)

**Antimicrobial Resistance**

Emergence of Antimicrobial Resistance: Time between Regulatory Approval or Introduction to the Market

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  - Escherichia coli with plasmid-mediated mcr-1 gene that confers resistance to colistin (originally described in China)

**Global Distribution of Carbapenemases in Enterobacteriaceae, by Country and Region**

**Recovery of mcr-1–Expressing Resistant Enterobacteriaceae Isolates as of June 21, 2016**
Colistin and Polymyxin B

- Assumed an important role as "salvage therapy" for otherwise untreatable Gram-negative infections
- Emerging pharmacokinetic-pharmacodynamic data indicate that monotherapy is unlikely to generate plasma concentrations that are reliably efficacious
- Regrowth and the emergence of resistance with monotherapy are commonly reported even when concentrations exceed those achieved clinically
- Combination therapy has been suggested as a possible means of increasing antimicrobial activity and reducing the development of resistance


Most Dangerous Antibiotic-Resistant Bacteria

WHO Priority Pathogen List for R&D of New Antibiotics

- Priority 1: Critical
  - Enterobacteriaceae, carbapenem-resistant, ESBL-producing
    - *Pseudomonas aeruginosa*, carbapenem-resistant
  - *Acinetobacter baumannii*, carbapenem-resistant
    - Includes multidrug-resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters
    - Can cause severe and often deadly infections such as bloodstream infections and pneumonia
    - Resistant to a large number of antibiotics, including the best available antibiotics for treating multidrug-resistant bacteria

WHO Priority Pathogen List for R&D of New Antibiotics

- Priority 2: HIGH
  - *Enterococcus faecium*, vancomycin-resistant
  - *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate or resistant
  - *Helicobacter pylori*, clarithromycin-resistant
  - *Campylobacter spp.*, fluoroquinolone-resistant
  - *Salmonella*, fluoroquinolone-resistant
  - *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

- Priority 3: MEDIUM
  - *Streptococcus pneumoniae*, penicillin-susceptible
  - *Haemophilus influenzae*, ampicillin-resistant
  - *Shigella spp.*, fluoroquinolone-resistant

Released February 27, 2017

Factors Placing Hospitalized Patients at High Risk for Acquiring MDR Gram-Negative Bacteria

- 891 patients with monomicrobial MDR BSI at Duke University
  - 292 patients (33%) had BSI due to MDR pathogens and more likely to have:
    - History of transplant (19% versus 13%; P = 0.02)
    - Prior Gram-negative infection (46% versus 33%; P = 0.0003)
    - Hospital-acquired infection (35% versus 28%; P = 0.05)
- Most commonly isolated Gram-negative bacteria were:
  - *Escherichia coli* (37%; 330/891)
  - *Klebsiella pneumoniae* (19%; 166/891)
  - *Pseudomonas aeruginosa* (13%; 119/891)
- MDR phenotype was most common in *Escherichia coli* (50%) and *Citrobacter freundii* (44%)


Bloodstream Infections Caused by Multidrug-Resistant Gram-Negative Bacteria

- 891 patients with monomicrobial MDR BSI at Duke University
  - 292 patients (33%) had BSI due to MDR pathogens and more likely to have:
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    - Prior Gram-negative infection (46% versus 33%; P = 0.0003)
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  - *Klebsiella pneumoniae* (19%; 166/891)
  - *Pseudomonas aeruginosa* (13%; 119/891)
- MDR phenotype was most common in *Escherichia coli* (50%) and *Citrobacter freundii* (44%)

In patients with hospital-acquired BSI (n=296), mean inpatient costs higher in patients with MDR BSI ($136,945 versus $89,197; P = 0.02)

Factors associated with Gram-negative BSI inpatient costs

Increased Costs Associated with Bloodstream Infections Caused by MDR Gram-Negative Bacteria

- MDR BSI relative to non-MDR BSI were associated with increased mean inpatient costs ($59,266 versus $36,452)
  - Significant even after adjustments for patient demographics, medical comorbidities, and treatment factors
- Increased cost of MDR BSI stemmed primarily from increased length of hospital stay
- Patients with hospital-acquired infections were the primary drivers of the increased costs associated with the MDR phenotype
- MDR BSI were associated with recurrent BSI during the same hospital stay

MDR, multidrug-resistant (nonsusceptible to at least one agent in greater than or equal to 3 antimicrobial categories)
BSI, bloodstream infection

Increased Costs Associated with Bloodstream Infections Caused by MDR Gram-Negative Bacteria

Guidelines for Antibiotic Stewardship

Antibiograms and Rapid Diagnostics

- Antibiograms summarize the proportion of organisms that are susceptible to specific antimicrobials during a specific period of time, usually annually
- Antibiograms are often used by stewardship programs to:
  - make formulary decisions
  - develop guidelines for empiric therapy
  - monitor local resistance rates over time
- Microbiology laboratories are essential to stewardship programs by ensuring quality specimen collection, appropriate testing, implementation of rapid diagnostics, antimicrobial susceptibility testing, and data analysis

Ceftolozane-Tazobactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa* and ESBL-producing strains
- FDA approval in December 2014
  - Complicated Urinary Tract Infections (cUTI), including pyelonephritis
  - Complicated Intrabdominal Infections (cIAI) plus metronidazole
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)
- Dosage adjustment in patients with renal impairment (CrCl ≤50 mL/min) or ESRD on hemodialysis
- Most common adverse reactions (≥5% in either indication) are nausea, diarrhea, headache, and pyrexia

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship


Ceftolozane-Tazobactam
Current Availability of Susceptibility Tests

- Disks
  - NAR Disks: Hardy Diagnostics, commercially available FDA-approved devices
  - Etest (TREK): commercially available
- Gradient Strips
  - Breakpoints published in the package insert and latest CLSI document

- Panels
  - Vitek 2 SM: panels available and will undergo beta testing; anticipate commercial availability in May 2017, software updates started in March 2017
  - Phoenix (BD): expect commercial availability in late 2017/2018
  - Vitek (Beckman Coulter): expect commercial availability in late 2017/2018

Ceftazidime-Avibactam
Current Availability of Susceptibility Tests

- Approved Tests
  - KB Disks: from Hardy Diagnostics and BD
  - Custom Sensitive (ThermoFisher): FDA-approved, not yet available

- Tests in Development
  - Etest - RUO only available at http://www.mprtest.com
  - Etest expected approval Q2-4 2017

- Automated Tests
  - Vitek 2: Software validation Q1 2017, expected approval Q2 2018
  - Microscan (Beckman Coulter): expect commercial availability in mid 2018
  - Phoenix (BD): FDA-approved, but not available yet

Antibiotic Resistance Threats in the United States, 2013

<table>
<thead>
<tr>
<th>Gram-Negative Organism</th>
<th>Cases (0.3)</th>
<th>Deaths (%)</th>
<th>Threat Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL-producing Enterobacteriaceae</td>
<td>25,650 (1.92)</td>
<td>7.6 (2.48)</td>
<td>Sefistain</td>
</tr>
<tr>
<td>Multiresistant Pseudomonas aeruginosa</td>
<td>2,270 (0.16)</td>
<td>4.9 (0.92)</td>
<td>Sefistain</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae</td>
<td>450 (0.16)</td>
<td>2.6 (0.77)</td>
<td>Urgent</td>
</tr>
<tr>
<td>Multiresistant Acinetobacter spp.</td>
<td>700 (0.05)</td>
<td>0.0 (0.16)</td>
<td>Sefistain</td>
</tr>
</tbody>
</table>

Estimated annual incidence of infection caused by multidrug-resistant organisms

- Total: 1,349,766 cases and 22,840 deaths
- Multidrug-resistant carbapenems and enhanced extended-spectrum cephalosporins
- Multidrug-resistant carbapenems and extended-spectrum β-lactams

ESBL Phenotype Among Enterobacteriaceae
Isolates in United States Hospitals – 2014

Ambler Classification
Beta-lactamases

<table>
<thead>
<tr>
<th>Ambler Class</th>
<th>Beta-lactamase Type</th>
<th>Proteolytic Substrates</th>
<th>Representative Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Extended spectrum</td>
<td>Nocardia, Pseudomonas, Proteus spp.</td>
<td>TEM, SHV, CTX-M</td>
</tr>
<tr>
<td>B</td>
<td>Extended spectrum</td>
<td>Enterobacter calotrochum</td>
<td>AmpC, KPC, NDM, IMP, MIR, OXA</td>
</tr>
<tr>
<td>C</td>
<td>Extended spectrum</td>
<td>Citrobacter, Proteus, Providencia, Morganella, Serratia, Enterobacteriaceae</td>
<td>ESBL, CTX-M, CMY, NDM</td>
</tr>
<tr>
<td>D</td>
<td>Extended spectrum</td>
<td>Enterobacter calotrochum</td>
<td>AmpC, IMP, CLSI, VIM, IMP, NDM</td>
</tr>
</tbody>
</table>


Use of Non-carbapenem Beta-Lactams for the Treatment of ESBL Infections

**Ceftolozane-Tazobactam**
- Considerable proportion of ESBL isolates demonstrate susceptibility
- Organizations can produce multiple ESBLs simultaneously or have additional resistance mechanisms (e.g., AmpC, QMPS)
- "Inoculum effect" similar to ceftolozane
- Contradictory results in clinical trials between piperacillin-tazobactam versus carbapenems for invasive ESBL infections

Use of Newer Beta-Lactam Beta-Lactamase Inhibitors for the Treatment of ESBL Infections

**Ceftolozane-Tazobactam**
- Ceftolozane has good activity against Enterobacteriaceae, but limited activity against ESBLs
- Tazobactam is a potent, irreversible inhibitor of most ESBLs
- MIC<sub>50</sub> / MIC<sub>90</sub> for ESBL-producing strains of:
  - Enterobacteriaceae: 0.5 / 4 mg/L
  - Klebsiella pneumoniae: 4 / 32 mg/L
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

Use of Non-carbapenem Beta-Lactams for the Treatment of ESBL Infections

**Cefepime**
- Diminished efficacy with higher bacterial inoculum (IV, pneumonia, osteosarcoma)
- Failure to meet pharmacodynamic targets: inadequate dosing and/or internal schedules
- 
  - Reduced resistance (CLSI breakpoint at 8 mg/L, accounting for drug dosing)
  - Contribution of ESBL production and drug MIC towards efficacy remains controversial
  - Conflicting results in clinical trials between ceftazidime versus carbapenems for invasive ESBL infections

Use of Newer Beta-Lactam Beta-Lactamase Inhibitors for the Treatment of ESBL Infections

**Ceftolozane-Tazobactam**
- Tends to be more active in vitro against ESBL producers than ceftazidime-tazobactam
- MIC<sub>50</sub> / MIC<sub>90</sub> for ESBL-producing strains of:
  - Enterobacteriaceae: 0.5 / 3.2 mg/L
  - Klebsiella pneumoniae: 2 / 16 mg/L
- Clinical cures rates for ME patients:
  - 83.8% (196/236) for meropenem
  - 85.1% (349/410) all patients for Meropenem
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor


**Pseudomonas aeruginosa** Resistance Mechanisms
- **Mucoid layer**
  - *P. aeruginosa* has a mucoid layer outside the outer membrane: increased thickness of this layer
  - Outer membrane porins
    - Loss of porins inhibits antibiotic entry
  - Efflux pumps
    - *P. aeruginosa* can carry efflux pumps in outer membrane; when present, antibiotics can be pumped out the cell
  - Penicillin-binding protein (PBP) alterations
    - In penicillin layer: altered to prevent interaction of antibiotics with their targets
  - Beta-lactamase upregulation
    - Regulation of the chromosomal AmpC, involves a complex relationship between penicillin-binding proteins, beta-lactamases, and overexpression of the AmpC enzyme
    - In periplasmic space of the bacteria; able to break down beta-lactam antibiotics and/or beta-lactam inhibitors
Ceftolozane-Tazobactam

- Demonstrated potent IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1
  Pseudomonas aeruginosa (susceptible)  Polymyxin (susceptible)
  Nonsusceptible (ceftolozane and tazobactam) for injection, for intravenous use Prescribing Information. Merck & Co., Inc., Whitehouse Station, NJ. October 2016
  ≤ 4 / 4*
  2014;74:31
  
  Isolates displaying derepressed AmpC had ceftolozane-tazobactam MIC values ranging from 1 to 16 mg.1
  The development of high-level resistance to ceftolozane-tazobactam appears to occur efficiently only in a Pseudomonas aeruginosa mutator background, in which multiple mutations lead to overexpression and structural modifications of AmpC.
  Pseudomonas aeruginosa is able to adapt to efficacious beta-lactams, including newer cephalosporin ceftolozane, through a variety of mutations affecting its intrinsic beta-lactamase, AmpC.*

### Ceftolozane-Tazobactam Therapy*

**Respiratory Infections due to MDR Pseudomonas aeruginosa**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Prior Antibiotics</th>
<th>Clinical / Microbiological Outcomes</th>
<th>Susceptibilities (MIC, µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 y</td>
<td>male</td>
<td></td>
<td>Cure / Eradication</td>
<td>Ceftolozane-Tazobactam (2 g)&lt;br&gt;Meropenem (1 g)&lt;br&gt;Colistin (2 MBP)</td>
</tr>
<tr>
<td>65 y</td>
<td>female</td>
<td></td>
<td>Cure / Eradication</td>
<td>Ceftolozane-Tazobactam (2 g)&lt;br&gt;Meropenem (1 g)&lt;br&gt;Colistin (2 MBP)</td>
</tr>
<tr>
<td>52 y</td>
<td>male</td>
<td></td>
<td>Cure / Eradication</td>
<td>Ceftolozane-Tazobactam (2 g)&lt;br&gt;Meropenem (1 g)&lt;br&gt;Colistin (2 MBP)</td>
</tr>
</tbody>
</table>

* Ceftolozane-tazobactam 3 g IV every 6 hours for 14 days

- **Spectrum of activity:** Gram-negatives, including MDR Pseudomonas aeruginosa and ESBL-producing strains
  - FDA approval in December 2014
    - Complicated Urinary Tract Infections, including Pyelonephritis
    - Complicated Intrabdominal Infections (plus metronidazole)
    - IV dose: 1.6 (1 g ceftolozane; 0.5 g tazobactam) q8h (5 L infusion)
  - Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia increase dose: 3.0 g (2 g ceftolozane; 1 g tazobactam)<br>For 6 days; however 14 days for Pseudomonas aeruginosa
  - Plasma-to-epithelial lining fluid penetration ~50%
**“Real World” Treatment Reports**

**Ceftolozane-Tazobactam for MDR Pseudomonas aeruginosa**

- 15 patients with XDR infections: Clinic cure 67%; All-cause in-hospital mortality 27%; 6/8 microbiological cure; 2 microbiological failures; combination therapy in 10 of 15: 4 failures at end of therapy
- Multicenter, retrospective study of 10 patients infected with carbapenem-resistant *P. aeruginosa*; pneumonia most common indication (n=15); treatment success rate was 74% (n=28); treatment failure in all cases where MIC ≥8 mg/L
- Multicenter, retrospective study of 12 patients; salvage therapy for severe MDR infections

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**Ceftazidime-Avibactam**

- Demonstrated in vitro activity against *Pseudomonas aeruginosa* in the presence of:
  - some AmpC beta-lactamases or
  - certain strains lacking outer membrane porin (OmpC)
- Not active against bacteria producing metallo-beta-lactamases and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations
- Current FDA susceptibility interpretive criteria:

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Minimum Inhibitory Concentrations (mg/L)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤ 0.06/≤ 4 µg/mL</td>
<td>≥ 96</td>
</tr>
<tr>
<td>Entrobacteriaceae</td>
<td>≥ 0.12/≥ 4 µg/mL</td>
<td>≤ 4</td>
</tr>
</tbody>
</table>

---

**Resistance to Ceftazidime-Avibactam**

- beta-lactam-resistant *Pseudomonas aeruginosa* clinical isolates
  - 18.5% of archived isolates (n ≥ 54) from a decade ago were resistant to ceftazidime-avibactam with MIC of 216 µg/mL
- Acquired resistance, which may be driven by altered outer membrane permeability or overexpressed efflux pumps
- Combination poses a potential advantage
  - Addition of colistin reduced resistance to 7% of strains
  - Addition of fosfomycin reduced resistance to 1% of strains
- Resistance was not due to changes in penicillin-binding-protein (PBP) sequence or changes to beta-lactamase sequence or expression level

---

**Case Series from Compassionate-use**

- REPRISE Study
  - Ceftazidime-avibactam or best-available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* cUTI or cIAI
  - Randomized, open-label, pathogen-directed, phase 3 study
- Case Series from Compassionate-use
  - Ceftazidime-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*
  - EMA-approved indications also include:
    - Hospital-acquired pneumonia, including ventilator-associated pneumonia
    - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
    - Plasma-to-epithelial lining fluid penetration ~30%
Choice of antibiotics should be based on the local resistance epidemiology in infection site, pathogen, and usually appropriate empirically monotherapy. KPC- and Aminoglycosides are considered if high prevalence at the institution orResistance Enterobacteriaceae (CRE) Infections. Extensive use of combination therapy is under debate, as well as the optimal choice of agents when combinations are used.

Monotherapy vs Combination Therapy Carbapenem-Resistant Enterobacteriaceae (CRE) Infections

Outcomes of Patients Carbapenem-Resistant Klebsiella pneumoniae

Patients who received "inappropriate" therapy (A) (no agent was active in vitro) Combination therapy (C) with two or more in vitro active agents was superior to monotherapy (B) Carbapenem-containing combinations (C2) resulted in significantly lower mortality rates than the carbapenem-sparing combinations (C1)
Ceftazidime-Avibactam

Emergence of Resistance among Enterobacteriaceae

- First clinical case of a ceftazidime-avibactam-resistant Klebsiella pneumoniae, in a patient with no previous exposure.
- Resistance due to point mutations and the increased expression of KPC-2.
- 37 CRE-infected patients treated with ceftazidime-avibactam.
  - Clinical success was 39% (20/52) and 30-day survival was 70% (38/52).
  - CRE infection; recurred within 30 days (5/32).
- Resistance detected in 50% (20/40) of microbiologic failures.
- Development of resistance conferred blu80 mutations in K. pneumoniae within 10-19 days of ceftazidime-avibactam exposure, but may be ameliorated if carbapenem susceptibility is restored.
- Surveillance studies continue to document low frequency of ceftazidime q8h development of resistance conferring blu80.

Carbapenem plus Beta-Lactamase Inhibitor

- Vaborbactam (RPX7009)
  - Cyclic boronic acid-based beta-lactamase inhibitor.
  - Creates a covalent bond between boron moiety and active serine hydroxyl of a beta-lactamase.
  - Good affinity for many class A and C serine beta-lactamases.
  - High inhibitory potency against KPC-producing isolates.
  - Currently combined with meropenem.

- Relbebacat (MK-7655)
  - Dihydroxyboronic, non-beta-lactam, beta-lactamase inhibitor.
  - Similar chemical structure and spectrum of activity as avibactam.
  - Class A and C activity with minor D activity.
  - Lack of activity against MRSA and most Gram-positives.
  - Currently combined with imipenem-clavulanate.

In Vitro Activity: Meropenem-Vaborbactam

<table>
<thead>
<tr>
<th>Species</th>
<th>Meropenem</th>
<th>Meropenem-Vaborbactam 4 mg/L</th>
<th>Meropenem-Vaborbactam 8 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumoniae (KPC+) (121)</td>
<td>3</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Proteus mirabilis (IMI)</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Acinetobacter baumannii (IMI)</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
</tbody>
</table>

Meropenem-Vaborbactam

- Excellent in vitro activity against common Enterobacteriaceae species producing KPC-2 at a fixed concentration of vaborbactam of 8 mg/L.
- In vitro hollow-fiber model (simulating human exposure, 2 g meropenem + 2 g vaborbactam q8h 3h infusion) bactericidal against KPC-producing Enterobacteriaceae.
- In vivo efficacy in murine thigh infection model against K. pneumoniae, E. coli, and E. cloacae (MICs ranging from 0.06 to 0.5 mg/mL).
- Agents display identical concentration-time profiles in plasma and in ELF.
- Efficacy, Safety, Tolerability of CarbaVance Compared to Best Available Therapy in Serious Infections Due to Carbapenem-Resistant Enterobacteriaceae in Adults (TANGO 2) (EPI22038, clinicaltrials.gov).
- A Study of Meropenem-Vaborbactam versus Piperacillin-Tazobactam in Participants with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HAP/VAP) (NCT02187211, clinicaltrials.gov).

Agents Being Developed to Treat Resistant Gram-Negative Bacteria

<table>
<thead>
<tr>
<th>Agent</th>
<th>Related Class</th>
<th>Developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem-Vaborbactam</td>
<td>BLB/L</td>
<td>The Medicines Company</td>
</tr>
<tr>
<td>Relbebacat (MK-7655)</td>
<td>BLB/L</td>
<td>Merck</td>
</tr>
<tr>
<td>Aztreonam-Avibactam</td>
<td>BLB/L</td>
<td>Asta-Zeneca</td>
</tr>
<tr>
<td>Cefepime-Relbebacat</td>
<td>BLB/L</td>
<td>Wockhardt</td>
</tr>
<tr>
<td>Carbapenem-Cephalosporin</td>
<td>Cephalosporin</td>
<td>Shionogi</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Avante Healthcare</td>
</tr>
<tr>
<td>Ertapenem-Vaborbactam</td>
<td>Tazobactam</td>
<td>Tetragenex Therapeutics</td>
</tr>
<tr>
<td>Meropenem-ELIXA3214</td>
<td>ELIXA</td>
<td>Enterax Therapeutics</td>
</tr>
</tbody>
</table>

In Ongoing and Completed Clinical Trials:

4. Ertapenem-Vaborbactam, Elastin, and Merck (40.8% and 41.0%).
6. Ertapenem-Vavorbactam, Elastin, and Merck (40.8% and 41.0%).
**In Vitro Activity of Imipenem-Relebactam**

4,000 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014.

<table>
<thead>
<tr>
<th>Species</th>
<th>Imipenem</th>
<th>IMI 1</th>
<th>IMI 2</th>
<th>Relebactam</th>
<th>IMI 1+RBL</th>
<th>IMI 2+RBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii (AB)</td>
<td>8.0 (4/50)</td>
<td>6.5 (2/31)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
</tr>
<tr>
<td>Escherichia coli (E. coli)</td>
<td>8.0 (4/50)</td>
<td>6.5 (2/31)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (K. pneumoniae)</td>
<td>8.0 (4/50)</td>
<td>6.5 (2/31)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (P. aeruginosa)</td>
<td>8.0 (4/50)</td>
<td>6.5 (2/31)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
</tr>
<tr>
<td>Staphylococcus aureus (S. aureus)</td>
<td>8.0 (4/50)</td>
<td>6.5 (2/31)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
<td>6.0 (3/50)</td>
<td>7.5 (3/40)</td>
</tr>
</tbody>
</table>

MIC values in mg/L.

**Plazomicin (ACHN-490)**

- Next-generation aminoglycoside ("neoglycoside") synthetically derived from azlocillin.
- In vitro activity against both Gram-positive and Gram-negative organisms, including isolates harboring any of the clinically relevant aminoglycoside-modifying enzymes (e.g., acetyltransferases [AAC], nucleotidyltransferases [ANT], and phosphotransferases [APH]).
- Retains in vitro activity against aminoglycoside-resistant MDR, PDR, and ADR isolates of Enterobacteriaceae, except the New Delhi metallo-
- Plazomicin is not active against isolates that produce acquired 16S-RMNase.

**Plazomicin**

A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem Followed by Optimal Oral Therapy for the Treatment of Complicated Urinary Tract Infections, including Acute Pyelonephritis, in Adults

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pre-Patellar</th>
<th>Post-Patellar (PE Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRST Population</td>
<td>87.4% (147/168)</td>
<td>71.1% (114/160)</td>
</tr>
<tr>
<td>IMP Population</td>
<td>68.0% (105/156)</td>
<td>58.9% (91/155)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>80.0% (147/184)</td>
<td>77.0% (114/148)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>88.0% (136/155)</td>
<td>87.0% (126/145)</td>
</tr>
<tr>
<td>Total</td>
<td>89.0% (243/271)</td>
<td>79.5% (211/264)</td>
</tr>
</tbody>
</table>

**Multidrug-Resistant Acinetobacter spp. Isolates in United States Hospitals: 2011–2014**

<table>
<thead>
<tr>
<th>National resistance:</th>
<th>2011</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>% RESISTANT</td>
<td>54.5%</td>
<td>54.8%</td>
</tr>
<tr>
<td>% NON-RESISTANT</td>
<td>45.5%</td>
<td>45.2%</td>
</tr>
</tbody>
</table>

**Imipenem+Cilastatin and Relebactam (MK-7655A)**

- In vivo efficacy in murine, neutropenic, thigh infection model against imipenem-resistant Pseudomonas aeruginosa with OprD deficiency and expression of AmpC beta-lactamase and imipenem-resistant KPC-producing Klebsiella pneumoniae strains.
- Phase 2 complicated intraabdominal infections trial (n=351 patients):
  - Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=320).
- Efficacy and Safety of Imipenem+Cilastatin/Relebactam (MK-7655A) versus Colistimethate Sodium plus Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infections (RESTORE-IM 1)
  - Ongoing trial (NCT02452047, clinicaltrials.gov).
- Imipenem+Relebactam+Cilastatin versus Piperacillin/Tazobactam for Treatment of Participants with Bacterial Pneumonia (RESTORE-IM 2)
  - Ongoing trial (NCT02493764, clinicaltrials.gov).

**Imipenem-Cilastatin**

ECCMID, Vienna, Austria 2017; Abstract OS0250F.

Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230).

**Plazomicin**

ECCMID, Vienna, Austria 2017; Abstract OS0250E.

Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230).

**Relebactam**

ECCMID, Vienna, Austria 2017; Abstract OS0250D.

Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230).

**Plazomicin**

ECCMID, Vienna, Austria 2017; Abstract OS0250C.

Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230).

**Imipenem+Cilastatin**

ECCMID, Vienna, Austria 2017; Abstract OS0250B.

Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230).

**Imipenem**

ECCMID, Vienna, Austria 2017; Abstract OS0250A.

Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230).
Minocycline and tigecycline are tetracycline derivatives with antibacterial activity. Tigecycline is a fully synthetic fluorocycline with broad-spectrum activity, including MDR Gram-positive, Gram-negative, aerobic and anaerobic organisms (reduced activity against Pseudomonas aeruginosa and Acinetobacter baumannii). Tigecycline is active against isolates containing tetracycline-resistant TetO and TetM, and ribosomal protection proteins (TetX and TetD).

Muropepavadin (POL7080) is a fully synthetic cephalosporin with a catechol moiety and binds mainly to FEP-3 of Gram-negative bacteria. Muropepavadin's superior in vitro activity than beta-lactam comparators against ESBL-, KPC- or metallo-beta-lactamase-positive Enterobacteriaceae isolates, and both MDR P. aeruginosa and A. baumannii strains.

Agents Targeting a Single MDR Pathogen

- Sulbactam - ETX2514
  - ETX2514 is a broad-spectrum and potent inhibitor of class A, C, and D beta-lactamases
  - Sulbactam is a beta-lactam agent that has intrinsic activity against Acinetobacter baumannii (but widespread beta-lactamase-mediated resistance to sulbactam)
- Muropepavadin (POL7080)
  - Pseudomonas-specific antibiotic, with a novel mode of action
  - Being developed for the treatment of the most severe Pseudomonas aeruginosa infection – nosocomial pneumonia (including VABP and HABP)

In Vitro Activity of Eravacycline

- Fully synthetic fluorocycline with broad-spectrum activity, including MDR Gram-positive, Gram-negative, aerobic and anaerobic organisms (reduced activity against Pseudomonas aeruginosa and Acinetobacter baumannii). Eravacycline is active against isolates containing tetracycline-specific efflux (TetX and TetD) and ribosomal protection proteins (TetA and TetB).

Cefiderocol (S-649266)

- Slender cephalosporin with a catechol moiety and binds mainly to FEP-3 of Gram-negative bacteria
- Cefiderocol is a beta-lactam antibiotic that has intrinsic activity against Acinetobacter baumannii and A. baumannii strains

Cefiderocol (S-649266)

- Completed Trial (top-line results)

- Ongoing Trials:
  - Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Enterobacteriaceae (NCT03032380; ClinicalTrials.gov) {not yet recruiting}

Antibiotic Treatment of Multidrug-Resistant Gram-Negative Organisms

- Multidrug-resistant Gram-negative bacteria have become widespread and increasing worldwide
- New agents for treatment of Gram-negative infections are promising and could help preserve and enhance our antibiotic armamentarium
- Choice of empiric therapy has become more difficult for serious infections because of antimicrobial resistance to first-line agents
- Clinicians also have the dilemma between choosing:
  - an agent that is inactive versus a broad-spectrum agent
  - monotherapy versus combination therapy
  - determining the role of adjunctive therapy