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:

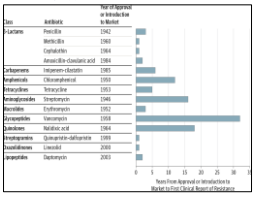
- Discuss current epidemiological trends regarding multidrug-resistant (MDR) Gram-negative bacteria and their impact on clinical outcomes
- Summarize approaches aimed at minimizing the spread and development of antimicrobial resistance, including antimicrobial stewardship strategies and rapid diagnostic 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

Antimicrobial Resistance

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

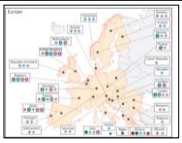


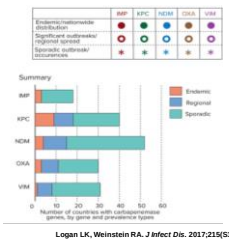
AMR, Antimicrobial Resistance

Marston HD, et al. *JAMA*. 2016; 316: 1193-1204.

- **In USA:**
  - **AMR organisms cause >2 million infections**
  - **23,000 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 bla_{NDM-1} gene that confers resistance to carbapenems)**
  - ***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





Logan LK, Weinstein RA. *J Infect Dis*. 2017;215(S1):S28-S36.

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

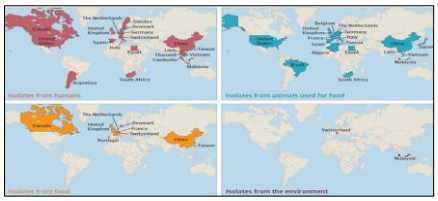


Figure depicts the identification of *mcr-1*–expressing isolates from various specimen types (human, animals used for food, food, environment) by country.

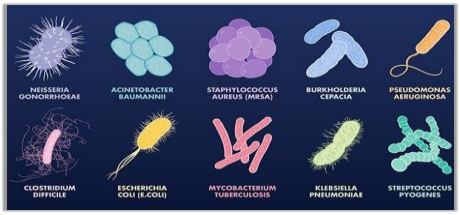
Marston HD, et al. *JAMA*. 2016;316:1193-1204.

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**

Bergen PJ, et al. *Pharmacother.* 2015;356:34-42.

Most Dangerous Antibiotic-Resistant Bacteria



Longitude Prize. Available at: https://longitudeprize.org/blog-post/10-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**

Released February 27, 2017
WHO. Available at: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/.

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**
  - ***Salmonellae*, fluoroquinolone-resistant**
  - ***Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant**
- **Priority 3: MEDIUM**
  - ***Streptococcus pneumoniae*, penicillin-non-susceptible**
  - ***Haemophilus influenzae*, ampicillin-resistant**
  - ***Shigella* spp., fluoroquinolone-resistant**

Released February 27, 2017
WHO. Available at: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/.

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

High Risk of Resistance	High Risk of Mortality
• Institutional MDR bacteria (endemic or epidemic)	• Neutropenic with bacteremia
• Personal history of MDR pathogens	• Severe sepsis / septic shock
• Sepsis already present on antimicrobial therapy	• Burns
• Transplantation or neutropenia on prophylactic antimicrobial therapy	• Antimicrobial therapy in the past 90 days
• Cystic fibrosis	

Cerceo E, et al. *Microbial Drug Resistance.* 2016;22:412-431.

Bloodstream Infections Caused by Multidrug-Resistant Gram-Negative Bacteria

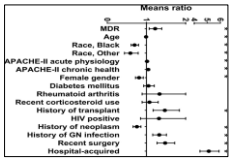
- **891 patients with monomicrobial MDR BSI at Duke University**
  - **292 patients (33%) had BSI due to MDR pathogens and more likely to have:**
    - **History of transplant (19% versus 13%; *P* = 0.02)**
    - **Prior Gram-negative infection (46% versus 33%; *P* = 0.0003)**
    - **Hospital-acquired 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%)**

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

Thaden JT, et al. *Antimicrob Agents Chemother.* 2017;61:e01709-16.

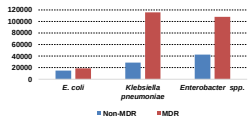
Increased Costs Associated with Bloodstream Infections Caused by MDR Gram-Negative Bacteria

Factors associated with Gram-negative BSI inpatient costs



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)

Inpatient Costs by Pathogen and MDR Status



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

Thaden JT, et al. *Antimicrob Agents Chemother.* 2017;61:e01709-16.

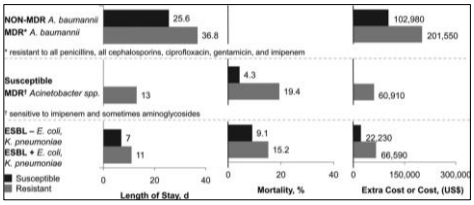
Increased Costs Associated with Bloodstream Infections Caused by MDR Gram-Negative Bacteria

- **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 infections

Thaden JT, et al. *Antimicrob Agents Chemother.* 2017;61:e01709-16.

Influence of Multidrug Resistance by Various Gram-Negative Bacteria



Sipahi OR. *Expert Rev Anti Infect.* 2008;6:523-539.
Cerceo E, et al. *Microbial Drug Resistance.* 2016;22:412-431.

Guidelines for Antibiotic Stewardship


Clinical Infectious Diseases
IDSA GUIDELINE

Bariam TF, et al. *Clin Infect Dis.* 2016;62:e51-e76.

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

GUIDELINES

Dellit TH, et al. *Clin Infect Dis.* 2007;44:159-177.

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

Avdic E, Carroll KC. *Infect Dis Clin North Am.* 2014;28:215-235.

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 Intraabdominal 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**

Scott LJ. *Drugs.* 2016;76:231-242.
Zhanel GG, et al. *Drugs.* 2014;74:31-51.
Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.

Ceftolozane-Tazobactam
Current Availability of Susceptibility Tests

- **Disks**
  - MAST Disk: Hardy Diagnostics, commercially-available FDA-approved diameters:
    - Enterobacteriaceae: >21mm (S), 18-20mm (I), and <17mm (R)
    - *P. aeruginosa*: >21mm (S), 17-20mm (I), and <16mm (R)
- **Gradient Strips**
  - Breakpoints published in the package insert and latest CLSI M100 document
    - Etest (Biomérieux) Research use only, Etests can be ordered from IHMA (http://mist-ruo.com) - Approval anticipated in June/July 2017
    - MIC test strip (Liofilchem) C/T test strips can be ordered directly from Liofilchem (http://www.liofilchem.net/en/pdf/mic_brochure.pdf). Approved in USA, Europe, Canada
- **Panels**
  - Vitek 2 (Biomérieux) card approved and will undergo beta-testing; anticipate commercial availability in May/June 2017, software updates started in March 2017
  - Microscan (Beckman Coulter) expect commercial availability in late 2017/2018
  - Phoenix (BD) expect commercial availability late 2017/2018
  - Trek Panel (ThermoFisher Scientific) commercially available since Q1 2016

Ceftazidime-Avibactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, and KPCs
- FDA approval in February 2015 (originally based Phase 2 data)
  - Complicated Urinary Tract Infections (cUTI), including pyelonephritis
  - Complicated Intraabdominal Infections (cIAI) *plus* metronidazole
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
- Dosage adjustment in patients with CrCl ≤50 mL/min
- Most common adverse reactions in cIAI (≥5%) patients are diarrhea, nausea, and vomiting. The most common (3%) in cUTI patients are diarrhea and nausea.

Zhanel GG, et al. *Drugs.* 2013;73:159-177.
Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.

Ceftazidime-Avibactam
Current Availability of Susceptibility Tests

- **Approved Tests**
  - KB Disks from Hardy Diagnostics and BD
  - Custom Sensititre (ThemoFisher)
- **Tests in Development**
  - Etest - RUO only available at www.avvcazeval.com
  - Etest expected approval Q3-4 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

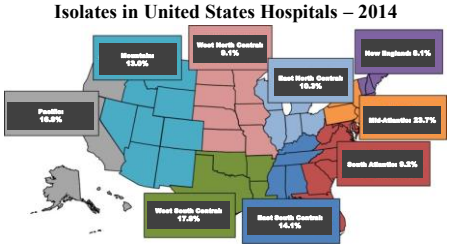
Antibiotic Resistance Threats
in the United States, 2013

Gram-Negative Organism	Cases (%)	Deaths (%)	Threat Level
ESBL-producing Enterobacteriaceae	26,000 (1.93)	1700 (7.44)	Serious
Multidrug-resistant *Pseudomonas aeruginosa*	6700 (0.5)	440 (1.92)	Serious
Carbapenem-resistant Enterobacteriaceae	9300 (0.69)	610 (2.67)	Urgent
Multidrug-resistant *Acinetobacter* spp.	7300 (0.54)	500 (2.18)	Serious

Estimated annual incidence of infection due to notable antimicrobial-resistant organisms
Total: 1,349,766 cases and 22,840 deaths
ESBL, extended-spectrum beta-lactamase

Thabit AK, et al. *Expert Opin Pharmacother.* 2015;16:159-177.
Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

ESBL Phenotype Among Enterobacteriaceae
Isolates in United States Hospitals – 2014



Castanheira M, et al. *Antimicrob Agents Chemother.* 2016;60:4770-7.

Ambler Classification
Beta-lactamases

Ambler Class	Beta-lactamase Type	Preferred Substrates	Representative Enzymes
A	Narrow-spectrum	Penicillins, narrow-spectrum cephalosporins	TEM-1, TEM-2, SHV-1
A	Extended-spectrum	Narrow and extended-spectrum beta-lactams	SHV-2, CTX-M-15, PER-1, VEB-1
A	Serine-carbapenemase	Carbapenems	KPC-1, IMI-1, SME-1
B	Metallo-beta-lactamases	Most beta-lactams, including carbapenems	VIM-1, IMP-1, NDM-1
C	Cephalosporinases	Cephalosporins	AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
D	OXA-type enzymes	Penicillins, oxacillins, carbapenems	OXA enzymes

Drawz SM, Bonomo RA. *Rev Clin Microbiol Rev.* 2010;14:160-201.
Toussaint KA, Gallagher JC. *Ann Pharmacother.* 2015;49:86-98.

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

Cefepime

- Diminished efficacy with higher bacterial inoculums (cIAI, pneumonia, osteoarticular)
- Failure to meet pharmacodynamic targets: inadequate dosing and/or interval schedules
- 'Hidden 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 cefepime versus carbapenems for invasive ESBL infections

Piperacillin-Tazobactam

- Considerable proportion of ESBL isolates demonstrate susceptibility
- Organisms can produce multiple ESBLs simultaneously or have additional resistance mechanisms (e.g., AmpC, OMP)
- "Inoculum effect" similar to cefepime
- Contradictory results in clinical trials between piperacillin-tazobactam versus carbapenems for invasive ESBL infections
  - High inoculum, higher median MIC, greater proportion of *Klebsiella pneumoniae* isolates
  - Underdosing of piperacillin-tazobactam

Tamma PD, Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-80.

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

- **Cefepime**
  - Do not favor use for serious ESBL infections
  - Nonsevere ESBL infections (e.g., UTIs with cefepime MICs ≤2 mg/L) so pharmacodynamics targets are met
  - Nonsevere ESBL-producing infections with MICs of 4–8 mg/L, recommend 2 g q8h, possibility as a continuous infusion
- **Piperacillin-Tazobactam**
  - Reasonable options for low- to moderate-severity infections resulting from urinary or biliary sources, and infections with piperacillin MIC <4 mg/L
  - Carbapenem may be more appropriate first in critically ill patients, patients with high inoculum infections, and elevated piperacillin MIC values
  - Regardless, recommend administering 4.5 g q6h (or 4.5 g q8h as extended infusion) for patients with invasive ESBL infections

Tamma PD, Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-80.

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_{50} / MIC_{90} for ESBL-producing strains of:
  Escherichia coli: 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

Tamma PD, Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-80.

- Efficacy of ceftolozane-tazobactam (C-T), pooled analysis Phase 3 cUTI & cIAI trials
- 150 patients (11%) had ESBL-producing Enterobacteriaceae (pooled ME population)
- MIC_{50} / MIC_{90} for 159 ESBL-producing strains:
  Ceftolozane-Tazobactam: 0.5 / 8 mg/L (81.8% S)
  Piperacillin-Tazobactam: 8 / 128 mg/L (73.0% S)
  Cefepime: 32 / 64 mg/L (19.6% S)
- Clinical cure rates for ME patients:
  98.0% (49/50) ESBL - *Escherichia coli* for C-T
  94.4% (17/18) ESBL – *K. pneumoniae* for C-T
  82.6% (38/46) for levofloxacin
  88.5% (23/26) for meropenem

Popejoy MW, et al. *J Antimicrob Chemother.* 2017;72:268-272.

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

Ceftazidime-Avibactam

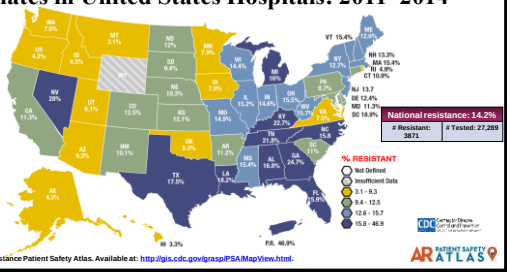
- Tends to be more active *in vitro* against ESBL producers than ceftolozane-tazobactam
- MIC_{50} / MIC_{90} for ESBL-producing strains of:
  Escherichia coli: 0.12 / 0.25 mg/L
  Klebsiella pneumoniae: 0.5 / 1 mg/L
- Showed similar microbiological response as doripenem against ceftazidime-resistant Enterobacteriaceae, most being ESBL-producing in cUTI study
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

Tamma PD and Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-980.

- Efficacy of ceftazidime-avibactam (Cef-Avi) among mMITT population Phase 3 cIAI trials
- 124 patients had Enterobacteriaceae after testing MIC screen positive (ceftriaxone and/or ceftazidime MIC >2 mg/L)
- Clinical cure rates for mMITT patients:
  87.5% (49/56) MIC-screen positive for Cef-Avi
  86.5% (64/74) MIC-screen positive for Meropenem
  92.5% (37/40) ESBL - ENT for Cef-Avi
  84.9% (45/53) ESBL - ENT for Meropenem
  81.6% (337/413) all patients for Cef-Avi
  85.1% (349/410) all patients for Meropenem

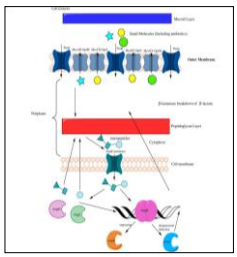
ENT, Enterobacteriaceae
Mendes RE, et al. *Antimicrob Agents Chemother* 2017; Epub doi.10.1128/AAC.02447-16.

Multidrug-Resistant *Pseudomonas aeruginosa* Isolates in United States Hospitals: 2011–2014



CDC Antibiotic Resistance Patient Safety Atlas. Available at: http://gis.cdc.gov/grasp/PSAMapView.html.

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-blinding protein (PBP) alterations
  - In peptidoglycan layer; altered to prevent interaction of antibiotics with their targets
- Beta-lactamase upregulation
  - Regulation of the chromosomal AmpC, involves a complex relationships between peptidoglycan breakdown, beta-lactam exposure, and overexpression of the AmpC enzyme
  - In periplasmic space of the bacteria; able to break down beta-lactam antibiotics and/or beta-lactamase inhibitors

Winkler ML, et al. *Antimicrob Agents Chemother.* 2015;59:1020-9.

Ceftolozane-Tazobactam

- Demonstrated potent *in vitro* activity against *Pseudomonas aeruginosa* isolates tested that had:
  - Chromosomal AmpC *or*
  - Loss of outer membrane porin (OprD) *or*
  - Up-regulation of efflux pumps (MexXY, MexAB)
- Not active against bacteria producing metallo-β-lactamases
- Current FDA susceptibility interpretive criteria:

	Minimum Inhibitory Concentrations (mg/L)		
Pathogen	Susceptible (S)	Intermediate (I)	Resistant (R)
Pseudomonas aeruginosa	≤ 4 / 4*	8 / 4*	≥ 16 / 4*

* Ceftolozane / tazobactam susceptibility testing performed with a fixed 4 μg/mL concentration of tazobactam

ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use Prescribing Information. Merck & Co., Inc., Whitehouse Station, NJ. October 2016
Takeda S, et al. *Int J Antimicrob Agents.* 2007;30:443-5.; Takeda S, et al. *Antimicrob Agents Chemother.* 2007;51:826-30.;
Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-50.

Ceftolozane-Tazobactam

Antimicrobial susceptibility patterns of 3851 *Pseudomonas aeruginosa* isolates from United States hospitals (PACTS, 2012–2015):

	% Susceptible	MIC_{50}	MIC_{90}
Ceftolozane-tazobactam	97.0	0.5	2
Amikacin	96.9	2	8
Cefepime	85.9	2	16
Ceftazidime	85.1	2	32
Colistin	99.2	1	2
Levofloxacin	76.6	0.5	>4
Meropenem	81.8	0.5	8
Piperacillin-tazobactam	80.4	4	>64

MIC (mg/L), minimal inhibitory concentration to inhibit growth of 50% and 90% of isolates

The MIC_{90} remained below the susceptible breakpoint of ≤4.0 mg/L for the 4-year period:

Year	%S	MIC_{50}	MIC_{90}
2015	98.0	0.5	1
2014	96.4	0.5	2
2013	96.4	0.5	2
2012	97.5	0.5	2

Shortridge D, et al. *Antimicrob Agents Chemother.* 2017;doi:10.1128/AAC.00465-17.

Ceftolozane-Tazobactam

Ceftolozane-tazobactam susceptibility patterns of 3851 *Pseudomonas aeruginosa* isolates from United States hospitals (PACTS, 2012–2015):

	% Susceptible	MIC_{50}	MIC_{90}
All isolates (n=3851)	97.0	0.5	2
Meropenem - Nonsusceptible (n=699)	87.6	1	8
Multidrug-resistant (MDR) (n=607)	84.0	2	8
Extensively drug-resistant (XDR) (n=363)	76.9	2	16
Nonsusceptible to cefepime, ceftazidime, meropenem, and piperacillin-tazobactam (n=241)	68.0	4	>32

Shortridge D, et al. *Antimicrob Agents Chemother* 2017; doi:10.1128/AAC.00465-17

Ceftolozane-Tazobactam

- Isolates displaying derepressed AmpC had ceftolozane-tazobactam MIC values ranging from 1 to 16 mg/L[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[2]
- *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[3]

[1] Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-55.
[2] Cabot G, et al. *Antimicrob Agents Chemother.* 2014;58:3091-9.
[3] Berrazeg M, et al. *Antimicrob Agents Chemother.* 2015;59:6248-55.

Ceftolozane-Tazobactam

- 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 Intraabdominal Infections (plus metronidazole)
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)
- Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia
  ***Increase dose*: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h**
  - For 8 days; however 14 days for *Pseudomonas aeruginosa*
- Plasma-to-epithelial lining fluid penetration ~50%

Zhanel GG, et al. *Drugs.* 2014;74:31-51.
Chandorkar G, et al. *J Antimicrob Chemother.* 2012;67:2463-9.
ClinicalTrials.gov: NCT02070757

Ceftolozane-Tazobactam Therapy*

Respiratory Infections due to MDR *Pseudomonas aeruginosa*

Age; Sex	Prior Antibiotics	Clinical / Microbiologic Outcomes	Susceptibilities (MIC, μg/mL)
69 y; male	Ciprofloxacin	Cure / Eradication	Ceftolozane-Tazobactam (0.25) Meropenem (>8) Cefepime (8) Ciprofloxacin (>2) Tobramycin (<2) Piperacillin-Tazobactam (<16)
63 y; male	Meropenem, Ciprofloxacin	Cure / Eradication	Ceftolozane-Tazobactam (1) Meropenem (>8) Cefepime (>16) Ciprofloxacin (>2) Tobramycin (>8) Piperacillin-Tazobactam (>64) Colistin (susceptible) Polymyxin (susceptible)
52 y; male	Meropenem, Linezolid	Cure / Eradication	Ceftolozane-Tazobactam (1) Meropenem (>8) Cefepime (16) Ciprofloxacin (<0.5) Tobramycin (<2) Piperacillin-Tazobactam (>16)

* Ceftolozane-tazobactam 3 g IV every 8 hours for 14 days

Gelfand MS, Cleveland KO. *Clin Infect Dis.* 2015;61:853-5 [letter to editor].

"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[1]
- Multicenter, retrospective study of 35 patients infected with carbapenem-resistant *P. aeruginosa*; pneumonia most common indication (n=18); treatment success rate was 74% (n=26); treatment failure in all cases where MIC ≥8 mg/L [2]
- Multicenter, retrospective study of 12 patients; salvage therapy for severe MDR infections (83% presented as septic shock; 3 deaths); pneumonia in 6 patients (50%); microbiological eradication in 10 patients (83.3%) however 2 patients late reoccurrence with C-T resistant MDR-PA [3]

[1] Dinh A, et al. *Int J Animicrob Agents*. 2017;49:782-3.
[2] Munita JM, et al. *Clin Infect Dis*. 2017;[Epub ahead of print]. doi: 10.1093/cid/cix014
[3] Caston JJ, et al. *Antimicrob Agents Chemother*. 2017;61:e02136-16.

Ceftazidime-Avibactam

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

	Minimum Inhibitory Concentrations (mg/L)	
Pathogens	Susceptible (S)	Resistant (R)
Pseudomonas aeruginosa Enterobacteriaceae	≤ 8 / 4*	≥ 16 / 4*

- Ceftazidime / avibactam susceptibility testing performed with a fixed 4 µg/mL concentration of avibactam

AVYCAZ® (ceftazidime and avibactam) for injection, for intravenous use. Prescribing Information, Allergan USA, Inc., Irvine, CA. January 2017.

Ceftazidime-Avibactam

Antimicrobial susceptibility patterns of 7452 *Pseudomonas aeruginosa* isolates from United States hospitals (INFORM, 2012–2015):

	% Susceptible	MIC_{50}	MIC_{90}
Ceftazidime-avibactam	97.0	2	4
Ceftazidime	84.3	2	32
Cefepime	85.4	2	16
Piperacillin-tazobactam	80.5	4	>64
Meropenem	82.0	0.5	8
Ciprofloxacin	77.5	0.12	>4
Levofloxacin	74.9	0.5	>4
Gentamicin	88.3	≤ 1	8
Amikacin	97.0	2	8
Colistin	99.4	1	2

MIC (mg/L), minimal inhibitory concentration to inhibit growth of 50% and 90% of isolates
CLSI Criteria for susceptible

The MIC_{90} remained below the susceptible breakpoint of ≤8.0 mg/L for the 4-year period:

Year	%S
2015	98.0
2014	96.3
2013	96.8
2012	96.9

Sader HS, et al. *Antimicrob Agents Chemother*. 2017;61:e02252-16.

Ceftazidime-Avibactam

Ceftazidime-avibactam activity tested against *Pseudomonas aeruginosa* isolates

	Cumulative (%) inhibited at MIC in mg/L of:			MIC_{50} / MIC_{90}
	4	8	16	(mg/L)
All isolates (n=7452)	91.4	97.0	98.8	2 / 4
Ceftazidime – Nonsusceptible (n=1168)	59.9	81.0	92.2	4 / 16
Meropenem – Nonsusceptible (n=1341)	65.5	86.2	94.0	4 / 16
Piperacillin-tazobactam – Nonsusceptible (n=1449)	62.0	85.4	94.1	4 / 16
Levofloxacin – Nonsusceptible (n=1868)	75.1	90.4	95.8	4 / 8
Gentamicin – Nonsusceptible (n=873)	73.9	87.6	92.9	2 / 16
Amikacin – Nonsusceptible (n=224)	69.2	79.5	87.1	4 / 32
Colistin – Nonsusceptible (n=45)	86.7	88.9	95.6	2 / 16
Multidrug-resistant (MDR) (n=1151)	57.3	82.1	92.5	4 / 16
Extensively drug-resistant (XDR) (n=698)	46.0	75.8	92.4	8 / 32
Nonsusceptible to Meropenem, Ceftazidime, and Piperacillin-tazobactam (n=607)	42.5	71.2	88.4	8 / 32

Sader HS, et al. *Antimicrob Agents Chemother*. 2017;61:e02252-16.

Resistance to Ceftazidime-Avibactam

- β-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 ≥16 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 1.9% of strains
- Resistance was not due to changes in penicillin-binding-protein (PBP) sequence or changes to β-lactamase sequence or expression level

Winkler ML, et al. *Antimicrob Agents Chemother*. 2015;59:1020-9.

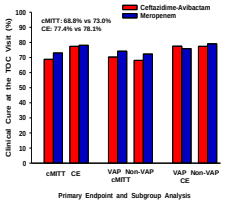
Ceftazidime-Avibactam

- REPRISE Study[1]
  - 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[2]
  - Carbapenem-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*
- EMA-approved indications also include:
  - Hospital-acquired pneumonia, including ventilator-associated pneumonia[3-5]
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
  - Plasma-to-epithelial lining fluid penetration ~30%[4]

1. Carmeli Y, et al. *Lancet Infect Dis*. 2016;16:661-73.
2. Temkin E, et al. *Antimicrob Agents Chemother*. 2017;61:e01964-16.
3. Liscio JL, et al. *Int J Antimicrob Agents*. 2015;46:266-71.
4. Nicolau D, et al. *J Antimicrob Chemother*. 2015;70:2862-9.
5. ClinicalTrials.gov: NCT01808092.

Nosocomial Pneumonia Including VAP

Phase 3, Randomized, Multicenter Study (REPROVE Study)



Secondary Efficacy Endpoints

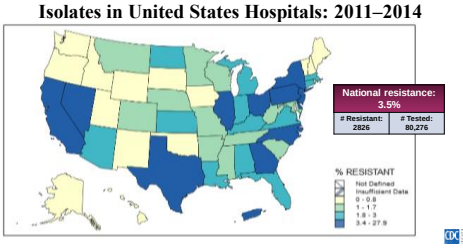
Per Pathogen Favorable Microbiological Response at TOC	Ceftazidime-Avibactam	Meropenem
mMITT		
K. pneumoniae	62.7% (37/59)	74.6% (53/71)
P. aeruginosa	37.9% (22/58)	38.3% (18/47)
eME		
K. pneumoniae	78.4% (29/37)	79.6% (39/49)
P. aeruginosa	42.9% (18/42)	40.0% (14/35)

TOC, test-of-cure; cMITT, clinically modified intent-to-treat; CE, clinically evaluable; mMITT, microbiological MITT; eME, extended microbiological evaluable

Presented at 27th ECCMID, Vienna, Austria 2017; Abstract OS0603
Results Reported: ClinicalTrials.gov: NCT01808092

Carbapenem-Resistant Enterobacteriaceae

Isolates in United States Hospitals: 2011–2014



CDC Antibiotic Resistance Patient Safety Atlas. Available at: http://gis.cdc.gov/grasp/PSA/MapView.html.

Commonly-Acquired Carbapenem-Hydrolyzing Beta-Lactamases in Enterobacteriaceae

Ambler Class	Active Site	Notable Gene	Retained Beta-Lactam Susceptibility
A	Serine	KPC GES	Carbapenems (low-to-high level hydrolysis) Carbapenems (low-level hydrolysis)
B	Zinc	VIM IMP NDM	Monobactams spared
D	Serine	OXA-48 OXA-181	Penicillin (high-level hydroloysis), Carbapenems (low-level hydrolysis), Extended-Spectrum Cephalosporins

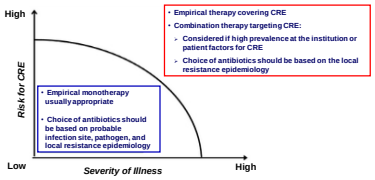
Logan LK, Weinstein RA. *Clin Infect Dis*. 2017;215 (Suppl 1):S28-S36.

Antibiotic Treatment of Carbapenem- Resistant Enterobacteriaceae (CRE)

- Treatment of infections with CRE is controversial because of paucity of convincing clinical data
- Clinical evidence regarding effectiveness of different treatment regimens is principally derived from retrospective studies, case reports, or small prospective studies; no randomized clinical trials
- Choice of agents often involves:
  - Aminoglycosides
  - Beta-lactam/beta-lactamase inhibitors
  - Carbapenems
  - Fosfomycin
  - Polymyxins
  - Rifampin
  - Tetracyclines
  - Tigecycline
- 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

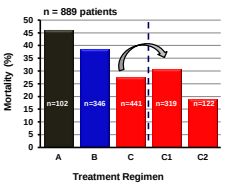


Tangden T, Giske CG. *J Intern Med*. 2015;277:501-12.

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)



Tzouvelekis LS, et al. *Clin Microbiol Infect*. 2014;20:862-72.

Ceftazidime-Avibactam

Emergence of Resistance among Enterobacteriaceae

- First clinical case of a ceftazidime-avibactam-resistant *Klebsiella pneumoniae*, in a patient with no previous exposure[1]
  - Resistance due to porin mutations and the increased expression of KPC-3[2]
- 37 CRE-infected patients treated with ceftazidime-avibactam[3]
  - Clinical success was 59% (22/37) and 30-day survival was 76% (28/37)
  - CRE infections recurred within 90 days in 23% (5/22)
  - Resistance detected in 30% (3/10) of microbiologic failures
  - Development of resistance conferring bla_{KPC-3} mutations in *K. pneumoniae* within 10 to 19 days of ceftazidime-avibactam exposure, but may be ameliorated if carbapenem susceptibility is restored[4]
- Surveillance studies continue to document low frequency of ceftazidime-avibactam resistance among Enterobacteriaceae isolates carrying bla_{KPC}[5,6]

1. Humphries RM, et al. *AAC*. 2015;59:6605-7.
2. Humphries RM, et al. *AAC*. 2017;61:doi:10.1128/AAC.00537-17.
3. Shields RK, et al. *Clin Infect Dis*. 2016;63:1615-8.
4. Shields RK, et al. *AAC*. 2017;61:e02097-16.
5. Castanheira M, et al. *AAC*. 2017;61:e02369-16.
6. Spellberg B, Bonomo RA. *Clin Infect Dis*. 2016;63:1619-21.

Agents Being Developed to Treat Resistant Gram-Negative Bacteria

Agent	Related Class	Developer
Meropenem-Vaborbactam	BLBLI	The Medicines Company
Imipenem-Relebactam	BLBLI	Merck
Aztreonam-Avibactam	BLBLI	Astra-Zeneca
Cefepime-Zidebactam	BLBLI	Wockhardt
Cefiderocol	Cephalosporin	Shionogi
Plazomicin	Aminoglycoside	Achaogen
Eravacycline	Tetracycline	Tetraphase
Murepavadin (POL7080)	Macrocycle LptD Inhibitor	Polyphor
Sulbactam-ETX2514	BLBLI	Entasis Therapeutics

BLBLI, Beta-lactam-beta-lactamase inhibitors combinations

Carbapenem plus Beta-Lactamase Inhibitor

- **Vaborbactam (RPX7009)**
  - Cyclic boronic acid-based beta-lactamase inhibitor
    - Creates a covalent bond between boron moiety and serine hydroxyl beta-lactamase
  - Good affinities for many class A and C serine beta-lactamases
    - High inhibitory potency against KPC-producing isolates
  - Currently combined with meropenem
- **Relebactam (MK-7655)**
  - Diazebicyclooctanone, non-beta-lactam, beta-lactamase inhibitor
  - Similar chemical structure and spectrum of activity as avibactam
    - Class A and C activity with minor D activity
    - Lacking activity against MBLs and most OXAs
  - Currently combined with imipenem-cilastatin

Falagas ME, et al. *Expert Rev Anti-Infect Ther.* 2016; 14: 747-63.
Papp-Wallace KM, Bonomo RA. *Infect Dis Clin North Am.* 2016;30:441-64.
Wong D, van Duin D. *Drugs*. 2017;77:615-28.

In Vitro Activity: Meropenem-Vaborbactam

- 4,500 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014

Species (n)	Meropenem		Meropenem-Vaborbactam (4 mg/L)		Meropenem-Vaborbactam (8 mg/L)	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Klebsiella pneumoniae (KPC+) (121)	8	64	0.06 / 4	2 / 4	0.03 / 8	0.5 / 8
Pseudomonas aeruginosa (96)	8	32	8 / 4	32 / 4	8 / 8	32 / 8
Acinetobacter baumannii (98)	32	64	32 / 4	64 / 4	32 / 8	64 / 8

MIC values in mg/L

- Addition of vaborbactam resulted in a 64- to 512-fold decrease in meropenem MIC in majority of KPC-positive isolates
- All but 2 of these isolates (98.3%) were inhibited by 1 mg/L meropenem combined with vaborbactam at 8 mg/L

Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:4856-60.

Meropenem-Vaborbactam

A Phase 3, Multi-Center, Randomized, Double-Blind, Double-Dummy Study to Evaluate the Efficacy, Safety, Tolerability of Carbavance (Meropenem/Vaborbactam) Compared to Piperacillin-Tazobactam in the Treatment of Complicated Urinary Tract Infections, including Acute Pyelonephritis, in Adults (TANGO 1) (NCT02166476; clinicaltrials.gov)

	EOVIT		Microbial Eradication at TOC	
mMITT Population	Meropenem-Vaborbactam	Piperacillin-Tazobactam	Meropenem-Vaborbactam	Piperacillin-Tazobactam
Overall	98.4%	94.0%	68.7%	57.7%
Acute Pyelonephritis	97.5%	94.1%	74.2%	63.3%
cUTI and Removable Source	100%	92.1%	60.0%	52.6%
cUTI and Non-Removable Source	100%	95.3%	48.6%	48.8%

Similar percentage of subjects with AP (59.2% and 59.0%) and cUTI (40.8% and 41.0%)
mMITT, Microbiological modified intent-to-treat
EOVIT, Overall success at end of IV treatment
TOC, Test of cure

Presented at 27th ECCMID, Vienna, Austria 2017; abstracts OS0604 and P1289.
Falagas ME, et al. *Expert Rev Anti-Infect Ther.* 2016;14:747-63.

Meropenem-Vaborbactam

- Excellent *in vitro* activity against common Enterobacteriaceae species producing serine carbapenemases 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 3-h infusion) bactericidal against KPC-producing Enterobacteriaceae
- *In vivo* efficacy in murine thigh infection model against KPC-producing isolates of *K. pneumoniae*, *E. coli*, and *E. cloacae* (MICs ranging from ≤0.06 to 8 µg/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)* Ongoing trial (NCT02168946; clinicaltrials.gov)
- *A Study of Meropenem-Vaborbactam versus Piperacillin-Tazobactam in Participants with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia* Not yet recruiting (NCT03006679; clinicaltrials.gov)

Presented at ICAAC 2014 (abstr. F-959 & F-958).
Falagas ME, et al. *Expert Rev Anti-Infect Ther.* 2016;14:747-63.
Wenzler E, et al. *Antimicrob Agents Chemother.* 2015;59:7232-9.
Griffith DC, et al. *Antimicrob Agents Chemother.* 2016;60:6326-32.
Castanheira M, et al. *Antimicrob Agents Chemother.* 2016;60:5454-8.

In Vitro Activity of Imipenem-Relebactam

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

Species (n)	Imipenem		Imipenem-Relebactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Escherichia coli (2778)	0.25	0.25	0.25 / 4	0.25 / 4
Klebsiella pneumoniae (891)	0.25	4	0.25 / 4	0.25 / 4
bla_{KPC}-possessing *K. pneumoniae* (111)	16	>16	0.25 / 4	1 / 4
Enterobacter spp. (211)	0.5	1	0.25 / 4	0.5 / 4
Pseudomonas aeruginosa (490)	2	16	0.5 / 4	2 / 4
Imipenem-resistant *P. aeruginosa* (144)	8	>16	1 / 4	2 / 4
Acinetobacter baumannii (158)	4	>16	2 / 4	>16 / 4
bla_{OXA-23}-possessing *A. baumannii* (58)	>16	>16	>16 / 4	>16 / 4

MIC values in mg/L

Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:5029-31.

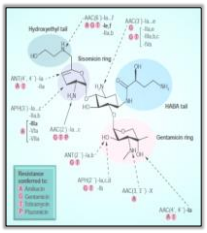
Imipenem+Cilastatin and Relebactam (MK-7655A)

- ***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):**
  - **1:1:1 ratio in treatment groups of relebactam 250 mg, 125 mg, placebo**
  - **Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable; n=230)**
- ***Efficacy and Safety of Imipenem + Cilastatin / Relebactam (MK-7655A) versus Colistimethate Sodium plus Imipenem + Cilastatin in Imipenem-Resistant Bacterial Infections (RESTORE-IMI 1)*** **Ongoing trial (NCT02452047; clinicaltrials.gov)**
- ***Imipenem/Relebactam/Cilastatin versus Piperacillin/Tazobactam for Treatment of Participants with Bacterial Pneumonia (RESTORE-IMI 2)*** **Ongoing trial (NCT02493764; clinicaltrials.gov)**

Mavridou E, et al. *Antimicrob Agents Chemother.* 2015;59:790-5.
Lucasti C, et al. *Antimicrobial Agents Chemother.* 2016;60:6234-43.
Falagas ME, et al. *Expert Rev Anti-Infect Ther.* 2016;14:747-63.

Plazomicin (ACHN-490)

- **Next-generation aminoglycoside ("neoglycoside") synthetically derived from sisomicin**
- ***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 XDR isolates of Enterobacteriaceae, except the New Delhi metallo-beta-lactamase (NDM) positive**
- **Plazomicin is not active against isolates that produce acquired 16S-RMTase**



Krause KM, et al. *Cold Spring Harb Perspect Med.* 2016;6(6).
Zhanel GG, et al. *Expert Rev Anti Infect Ther.* 2012;10:459-73.

Falagas ME, et al. *Expert Rev Anti Infect Ther.* 2016;14:747-63.
Doi Y, et al. *Infect Dis Clin North Am.* 2016;30:523-37.

Plazomicin

A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem Followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection, including Acute Pyelonephritis, in Adults **(NCT02486627, ClinicalTrials.gov)**

Outcome	Plazomicin	Meropenem	Difference (95% CI)
Per-Patient			
mMITT Population	87.4% (167/191)	72.1% (142/197)	15.4% (7.5, 23.2)
ME Population	90.5% (162/179)	76.6% (134/175)	13.9% (6.3, 21.7)
Per-Pathogen (ME Population)			
Enterobacteriaceae	90.3% (167/185)	77.5% (141/182)	12.8% (5.4, 20.4)
AG-non-susceptible	80.8% (42/52)	68.6% (35/51)	12.1% (-4.8, 28.7)
ESBL	83.3% (40/48)	74.6% (41/55)	8.8% (-7.5, 24.4)

Presented at the 27th ECCMID, Vienna, Austria 2017; Abstract OS0250E.

Plazomicin

A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE) [CARE] **(NCT01970371; ClinicalTrials.gov)**

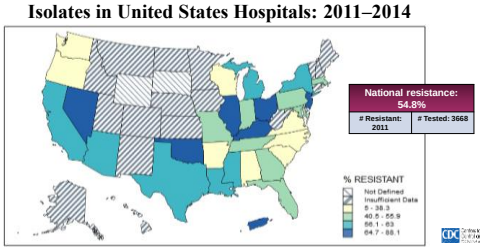
- **Plazomicin in combination with meropenem or tigecycline**
- **Colistin in combination with meropenem or tigecycline**
- **Treatment of patients with bloodstream infection, hospital-acquired or ventilator-associated bacterial pneumonia or complicated urinary tract infection**

	Plazomicin	Colistin	Difference (90% exact CI)	Relative Reduction
Day 28 ACM or SDRC	23.5% (4/17)	50.0% (10/20)	26.5% (-0.7, 51.2)	53.0%
Day 28 ACM	11.8% (2.17)	40.0% (8/20)	17.25% (0.7, 52.5)	70.5%

ACM, All-cause mortality
SDRC, Significant disease-related complications
Presented at 27th ECCMID, Vienna, Austria 2017; Abstract OS0250F.

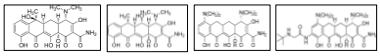
Multidrug-Resistant *Acinetobacter* spp.

Isolates in United States Hospitals: 2011–2014



CDC Antibiotic Resistance Patient Safety Atlas. Available at: http://gis.cdc.gov/grasp/PSA/MapView.html.

Tetracycline Antibiotics



Tetracycline | Doxycycline | Minocycline | Tigecycline

- Minocycline and tigecycline are tetracycline derivatives with antibacterial activity against *Acinetobacter baumannii* clinical isolates (including MDR and XDR strains)
- Exhibit additive or synergistic bactericidal activity against isolates when combined with other antibacterials
- Concerns with high mortality and increased recurrence of bacteremia when tigecycline MIC ≥2 mg/L

Greig SL, Scott LJ. *Drugs.* 2016;76:1467-76.
Lashinsky JN, et al. *Infect Dis Ther.* 2017; doi. 10.1007/s40121-017-0153-2.
Chuang YC, et al. *BMC Infect Dis.* 2014;14:102.
Cheng A, et al. *Crit Care Med.* 2015;43:1194-204.
Spellberg B, Bonomo RA. *Crit Care Med.* 2015;43:1332-4.

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 *Burkholderia cenocepacia*)
- Active against isolates containing tetracycline-specific efflux (TetA and TetB) and ribosomal protection proteins (TetM and TetO)
- Active against Enterobacteriaceae harboring ESBLs and carbapenemases

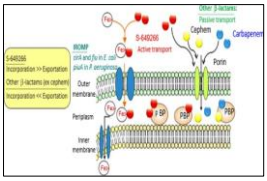
Species (n)	ESBL	bla_{KPC}	bla_{OXA}	Eravacycline MIC_{50}/MIC_{90}	Tigecycline MIC_{50}/MIC_{90}
E. coli (2,866)	13%	0.17%	-	0.12 / 0.5	4 / >16
K. pneumoniae (944)	33%	13%	-	0.25 / 1.0	0.5 / 2.0
Enterobacter aerogenes (90)	22%	3.3%	-	0.25 / 1.0	0.5 / 2.0
Enterobacter cloacae (124)	23%	3.2%	-	0.5 / 1.0	0.5 / 2.0
Acinetobacter baumannii (158)	67%	0.63%	36%	0.5 / 1.0	2.0 / 4.0

MIC values in mg/L

Abdallah M, et al. *Antimicrob Agents Chemother.* 2015;59:1802-5.

Cefiderocol (S-649266)

- Siderophore cephalosporin with a catechol moiety and binds mainly to PBP-3 of Gram-negative bacteria
- Catechol moiety to form a chelating complex with ferric iron
- 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



Ito-Horiyama T, et al. *Antimicrob Agents Chemother.* 2016;60:4384-6.
West KN, et al. *Antimicrob Agents Chemother.* 2016;60:729-34.
Ito A, et al. *J Antimicrob Chemother.* 2016;71:670-7.
Falagas ME, et al. *Expert Rev Anti Infect Ther.* 2016;14:747-63.
Tillotson GS. *Infect Dis (Auckl).* 2016;9:45-52.

Cefiderocol (S-649266)

- Completed Trial (top-line results) (NCT02321800; ClinicalTrials.gov)
  - *A Multicenter, Double-Blind, Randomized, Clinical Study to Assess the Efficacy and Safety of Intravenous S-649266 in Complicated Urinary Tract Infections with or without Pyelonephritis or Acute Uncomplicated Pyelonephritis Caused by Gram-Negative Pathogens in Hospitalized Adults in Comparison with Intravenous Imipenem/Cilastatin*

Outcome	Cefiderocol	Imipenem-Cilastatin	Difference (95% CI)
Clinical/Microbiological	72.6% (183/252)	54.6% (65/119)	18.58% (8.23, 28.92)
Per-Patient Microbiological	73.0% (184/252)	56.3% (67/119)	17.25% (6.92, 27.58)

- Ongoing Trials:
  - *Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-Negative Pathogens* (NCT02714595; ClinicalTrials.gov)
  - *Clinical Study of S-649266 for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens* (NCT03032380; ClinicalTrials.gov) (not yet recruiting)

Presented at the 27th ECCMID, Vienna, Austria 2017; Abstract OS0250D.
Falagas ME, et al. *Expert Rev Anti Infect Ther.* 2016;14:747-63.

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)
- Murepavadin (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)

Presented at the 27th ECCMID, Vienna, Austria 2017; Abstracts 4097, 5942, 1308-1311.
Srinivas N, et al. *Science.* 2010;327:1010-3.
Boucher HW, et al. *J Infect Dis.* 2017;[Epub ahead of print]: doi: 10.1093/infdis/jix211.

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