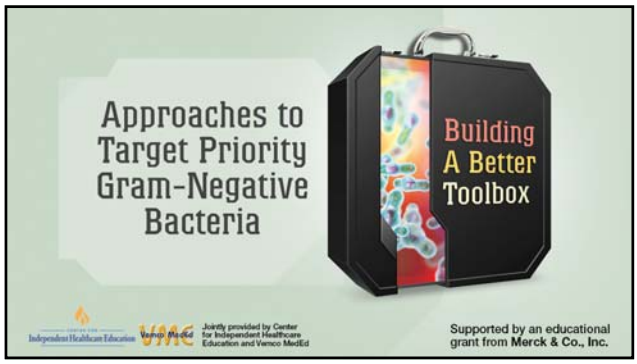

Activity Description

Target Audience
Addressing the challenges of priority Gram-negative 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 will target 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 and resistance mechanisms of priority Gram-negative bacteria and their impact on clinical outcomes
- Assess the value of rapid diagnostic techniques in promoting pathogen-specific therapy
- Evaluate the potential role of new and emerging antimicrobial agents in targeting antimicrobial-resistant Gram-negative pathogens

Faculty and Disclosure Statement (past 12 months)

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Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, IL

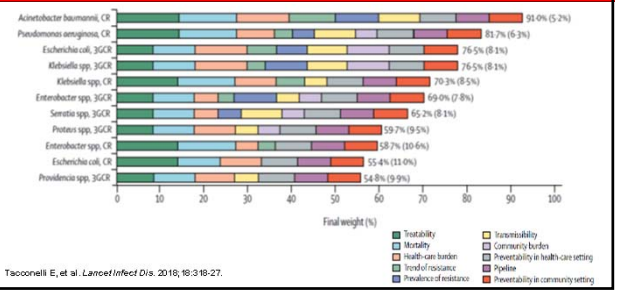
- ***Research Grants and Contracts:*** **Theravance Biopharma; Allergan; ARLG / NIAID / NIH**
- ***Consultant / Advisory Board:*** **Achaogen; Bayer; Entasis Therapeutics; GSK; Janssen Pharmaceuticals; Meiji; Melinta Therapeutics; The Medicines Company; Motif Bio PLC; Nabriva Therapeutics; Paratek; Shionogi; Spero Therapeutics; Theravance Biopharma; Tetraphase; Wockhardt; Zavante Therapeutics**
- ***Speaker's Bureau:*** **Merck & Co., Inc.; The Medicines Company**

Priority Lists
Gram-negative Pathogens

Centers for Disease Control – 2014 Urgent or Serious	World Health Organization – 2017 Priority 1: Critical
Carbapenem-resistant Enterobacteriaceae	Carbapenem-resistant Enterobacteriaceae
ESBL-producing Enterobacteriaceae	3rd-Generation Cephalosporin-Resistant Enterobacteriaceae
Multidrug-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Pseudomonas aeruginosa*
Multidrug-resistant *Acinetobacter* spp.	Carbapenem-resistant *Acinetobacter baumannii*

CDC. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
WHO. Available at: WHO. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1.

WHO Priority List
Final Ranking of Antibiotic-Resistant Bacteria



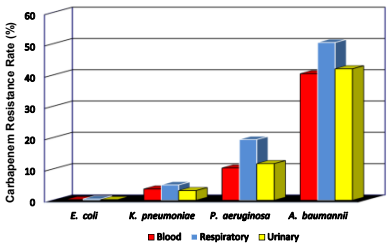
Tacconelli E, et al. *Lancet Infect Dis*. 2018;18:318-27.

Prevalence of Carbapenem-Resistant (CR) Gram-Negative Infections – USA 2009–2013

206 acute care hospitals
- **173,200 *E. coli***
- **56,552 *K. pneumoniae***
- **56,477 *P. aeruginosa***
- **6,508 *A. baumannii***

>80% of all CR infections caused by *A. baumannii* and *P. aeruginosa*

CR *P. aeruginosa* outnumbered *A. baumannii* by 3:1 in all regions except New England, where 85% were due to *P. aeruginosa*

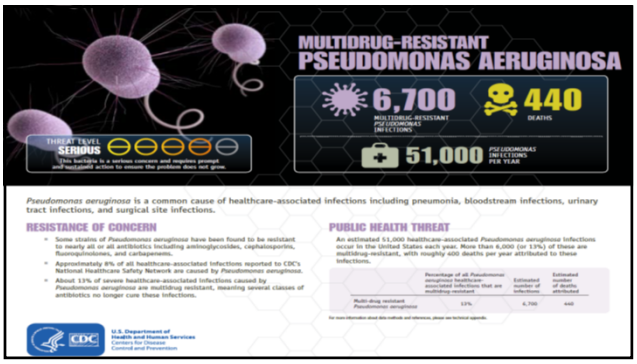


Cai B, et al. *Open Forum Infect Dis*. 2017;4:ofx176.

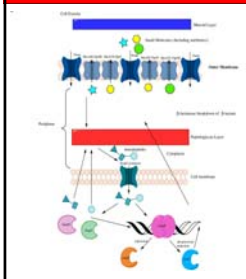
Multidrug-Resistant Pseudomonas aeruginosa
Isolates in United States Hospitals: 2011–2014

National resistance: 14.2%	
# Resistant: 3871	# Tested: 27,289

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

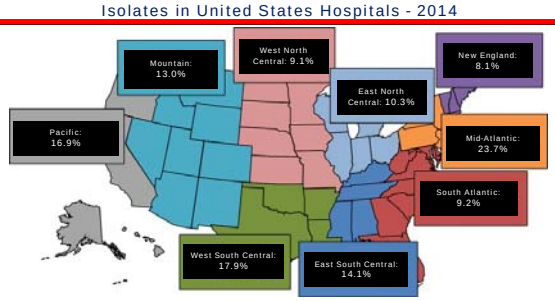
Efflux pumps
- *P. aeruginosa* can carry efflux pumps in outer membrane; when present, antibiotics can be pumped out the cell

Penicillin-binding 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;59:1020-1029.

ESBL Phenotype Among Enterobacteriaceae
Isolates in United States Hospitals - 2014

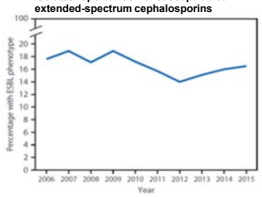


Castanheira M, et al. *Antimicrob Agents Chemother.* 2016;60:4770-4777.

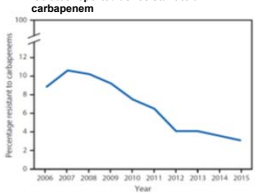
National Healthcare Safety Network
United States, 2006 - 2017

From selected healthcare-associated infections:
Central line-associated bloodstream and catheter-associated urinary tract infections

Percentage of *E. coli* and *K. pneumoniae* isolates reported as nonsusceptible to extended-spectrum cephalosporins

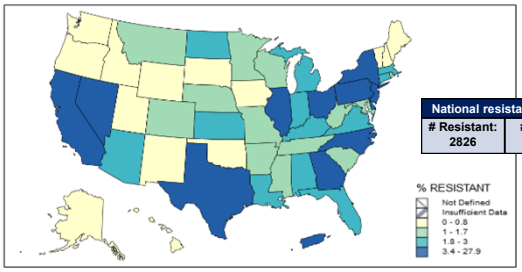


Percentage of *E. coli* and *K. pneumoniae* isolates reported as resistant to a carbapenem



Woodworth KR, et al. *MMWR.* 2018;67:396-401.

MDR Carbapenem-Resistant Enterobacteriaceae
Isolates in United States Hospitals: 2011–2014

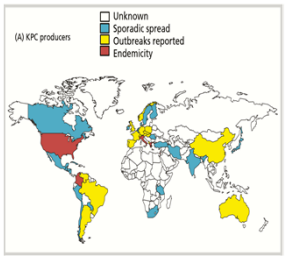


National resistance: 3.5%	
# Resistant: 2826	# Tested: 80,278

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

Worldwide Distribution of Carbapenemases

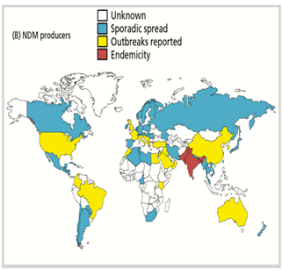
- The Class A *Klebsiella pneumoniae* carbapenemase (KPC) has been extensively reported in *K. pneumoniae* and other Enterobacteriaceae
- Has also been identified in other Gram-negative pathogens including *Pseudomonas aeruginosa*
- KPC-producing *Klebsiella pneumoniae* is widespread in the United States
- Endemic in some European countries such as Greece and Italy



Bonomo RA, et al. *Clin Infect Dis*. 2018;66:1290-1297.

Worldwide Distribution of Carbapenemases

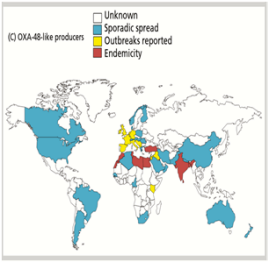
- Class B β-lactamases, or metallo-β-lactamases (MBLs): commonly identified in Enterobacteriaceae and *K. pneumoniae*
- Most frequently identified worldwide:
  - New Delhi (NDM)
  - Verona integrin-encoded (VIM)
  - Imipenemase (IMP)
- VIM most often found in Italy and Greece (Enterobacteriaceae) and in Russia (*P. aeruginosa*)
- IMP mainly detected in China, Japan, and Australia (mostly in *A. baumannii*)



Bonomo RA, et al. *Clin Infect Dis*. 2018;66:1290-1297.

Worldwide Distribution of Carbapenemases

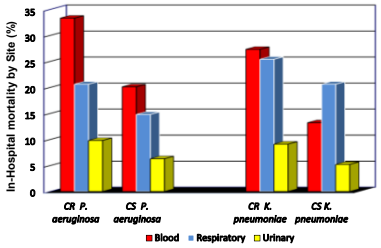
- Acquired Class D carbapenem-hydrolyzing β-lactamases: commonly reported in *A. baumannii*, but not in *P. aeruginosa*
  - Mainly oxacillinase [OXA]: OXA-24-, OXA-24/40-, and OXA-58-like enzymes
- OXA-48 and derivatives (OXA-181, OXA-232) are detected in Enterobacteriaceae
  - Hydrolyze narrow-spectrum β-lactamases and weakly hydrolyze carbapenems but spare broad-spectrum cephalosporins
- OXA-48-producing Enterobacteriaceae are endemic in Turkey and frequently encountered in several European countries (France, Belgium) and across North Africa



Bonomo RA, et al. *Clin Infect Dis*. 2018;66:1290-1297.

In-Hospital Mortality by Each Site

Carbapenem-Resistant (CR) vs -Susceptible (CS) Infections



Patients with CR pathogens were more likely to receive more than 1 systemic antibiotic

Patients with pathogens from the blood and respiratory were more likely to receive 2 or more antibiotics

Fewer different antibiotic combinations were used to treat patients with CS versus CR infections

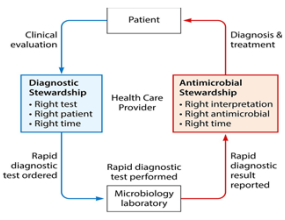
Cai B, et al. *Open Forum Infect Dis*. 2017;4:ofx176.

Implementation of Rapid Molecular Diagnostics

Role of Diagnostic and Antimicrobial Stewardship Programs

- Clinicians seek three basic truths from the clinical microbiology laboratory:
  - Whether the patient is infected?
  - If so, with what?
  - What will treat it?
- Molecular diagnostic technologies enable the microbiology laboratory to provide information faster and more accurately than ever before
- The 6 D's of antimicrobial stewardship:
  - Diagnosis
  - Debridement / drainage
  - Drug
  - Dose
  - Duration
  - De-escalation

Roles of Diagnostic Stewardship (DSP) and Antimicrobial Stewardship Programs (ASP)



Messacar K, et al. *J Clin Microbiol*. 2017;55:715-723.
Morency-Potvin P, et al. *Clin Microbiol Rev*. 2017;30:381-407.

Key Diagnostic Stewardship Considerations

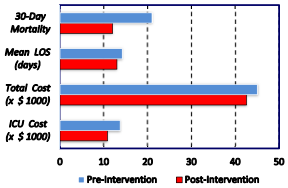
Implementation of Rapid Infectious Diseases Diagnostics

RIGHT TEST	*RIGHT PATIENT*	*RIGHT TIME*
Is the test appropriate for the clinical setting?	*Will the clinical care of the patient be affected by the test result?*	*Will the result be available in time to optimally affect care?*
• Sensitivity and specificity	• Laboratory test utilization committee	• Time to specimen receipt
• Predictive values	• Automatic laboratory reflex	• Centralized vs point-of-care testing
• Testing volumes	• CPOE decision support	• On-demand vs batched testing
• Diagnostic yield	• Appropriate use criteria	• Specimen preparation time
• Laboratory feasibility	• Indication selection	• Run time
• Cost	• Prior authorization	• Result reporting time
• Clinical impact	• Benchmarking	
	• Specimen rejection	

Messacar K, et al. *J Clin Microbiol*. 2017;55:715-723.

Value of Rapid Diagnostic Techniques
Added Cost - Is It Worth It?

Cost Analysis: Implementing MALDI-TOF MS plus Real-Time Antimicrobial Stewardship for BSIs



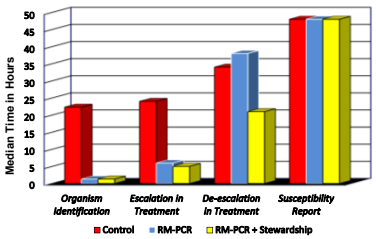
Conservative estimate of cost savings are lower than previous studies

- Included the cost of MALDI-TOF MS implementation for bacterial identification
- Cost of an antimicrobial stewardship pharmacist was included
- All bloodstream infections were included regardless of organisms
- An approximate annual cost savings of $ 2.34 million

MALDI-TOF MS, matrix-assisted laser desorption/ionization time of flight mass spectroscopy
Patel TS, et al. *J Clin Microbiol.* 2017;55:60-67.
TeKippe EM. *J Clin Microbiol.* 2017;55:20-23.

Randomized Trial of Rapid Multiplex PCR-Based Blood Culture Identification and Susceptibility Testing

- 617 patients with positive blood culture bottles
  - 207 Standard Processing (control)
  - 198 rmPCR (templated comments)
  - 212 rmPCR and Stewardship Team
- Stewardship impacted organism identification, escalation and de-escalation of antimicrobial therapy
- Both intervention groups had decreased broad-spectrum piperacillin-tazobactam and increased narrow-spectrum β-lactam use, and less treatment of contaminants



rmPCR, rapid multiplex polymerase chain reaction
Banerjee R, et al. *Clin Infect Dis.* 2015;61:1071-1080.

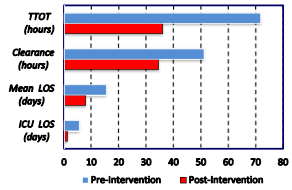
Key Antimicrobial Stewardship Considerations
Implementation of Rapid Infectious Diseases Diagnostics

RIGHT INTERPRETATION *Will the clinician understand the test result?*	*RIGHT ANTIMICROBIAL* *Will the clinician appropriately modify antimicrobials based on the result?*	*RIGHT TIME* *Will the clinician act upon the test result promptly?*
• Result report language • Selective reporting of relevant results • AS prospective audit and feedback • AS real-time decision support	• Clinical practice guidelines • EMR-based decision support with results reporting • AS prospective audit and feedback • AS real-time decision support	• EMR reporting • Results called with readback reporting • AS prospective audit and feedback • AS real-time decision support

AS, antimicrobial stewardship; EMR, electronic medical records
Messacar K, et al. *J Clin Microbiol.* 2017;55:715-723.

Value of Rapid Diagnostic Techniques
Time to Optimal Antimicrobial Therapy (TOTT)

Patients with Gram-Negative Infections: MALDI-TOF MS plus Real-Time Antimicrobial Stewardship [1]



Addition of the FilmArray Blood Culture Identification (BCID) Panel [2]

Outcome (days) [Median (IQR)]	MALDI-TOF MS + Stewardship	Addition of FilmArray BCID
Organism ID	1.7 [1.7-1.9]	0.8 [0.7-0.8]
De-escalation of Combination Tx	2.0 [1.0-2.8]	1.0 [1.0-2.0]
De-escalation of Antipseudomonal β-lactams	2.7 [2.5-3.0]	2.2 [2.0-2.5]
De-escalation of Carbapenems	2.8 [2.0-3.3]	2.1 [1.0-2.9]

[1] Beganovic M, et al. *J Clin Microbiol.* 2017;55:1437-1445.
[2] Bookstaver PB, et al. *Antimicrob Agents Chemother.* 2017;61:e00189-17.

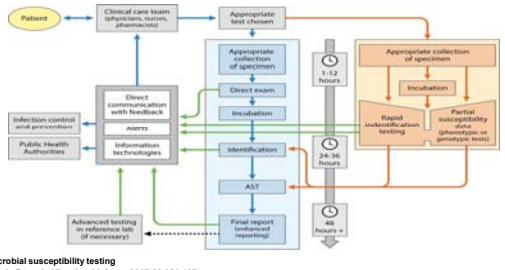
Value of Rapid Diagnostic Techniques
Safety of De-escalation

- 1046 Gram-negative bloodstream isolates from DMC (*n* = 765) and UMMC (*n* = 281) analyzed with the Verigene BC-GN platform
- Negative predictive values (NPVs) for ceftriaxone susceptibility in *Escherichia coli* and *Klebsiella pneumoniae* in the absence of either CTX-M or a carbapenemase gene were 98% and 94%, respectively
- NPVs of 94% to 100% were demonstrated for other target bug-drug scenarios, with the exception of *Pseudomonas aeruginosa*
- Provides a blueprint for other stewardship programs and confidence in de-escalation in the absence of resistance determinant detection

DMC, Detroit Medical Center
UMMC, University of Maryland Medical Center

Pogue J, et al. *Antimicrob Agents Chemother.* 2018;62:e02538-17.
Markley JD, et al. *Cur Infect Dis Rep.* 2017;19:17.

Workflow Pathways for Conventional Microbiology and Rapid Diagnostic Testing



AST, antimicrobial susceptibility testing
Morency-Potvin P, et al. *Clin Microbiol Rev.* 2017;30:381-407.

Types of Severe Infections Recommended for General Antimicrobial Development

Infection	Enrollment Criteria	Endpoint
Complicated Urinary Tract Infections (cUTI)	Risk factors plus symptoms plus pyuria	Resolution of symptoms and sterilization of urine
Complicated Intra-Abdominal Infections (cIAI)	Operative diagnosis	Resolution of baseline symptoms
Hospital-Acquired Bacterial Pneumonia (HABP)	Specific pulmonary symptoms	28-day all-cause mortality
Ventilator-Associated Bacterial Pneumonia (VABP)	Specific pulmonary symptoms	28-day all-cause mortality

Rex JH, et al. *Clin Infect Dis*. 2017;65:141-146.

Antimicrobial Drug Development: Pathway for Gram-Negative Pathogens

Complicated Urinary Tract Infections (cUTI)	Complicated Intra-Abdominal Infections (cIAI)	Hospital-Acquired Bacterial Pneumonia (HABP)
Ceftolozane-Tazobactam*	Ceftolozane-Tazobactam*	Ceftazidime-Avibactam
Ceftazidime-Avibactam*	Ceftazidime-Avibactam*	Ceftolozane-Tazobactam
Meropenem-Vaborbactam*	Eravacycline*	Imipenem-Relebactam*
Plazomicin*		Cefiderocol
Cefiderocol*		
Fosfomycin (IV)*		

Agents currently approved or in Phase 3 drug development programs
Yellow box indicates that agent has FDA-approval for listed body site of infection
* Primary approval for entry into the US market

Recently Approved Antimicrobial Agents

- Ceftolozane-Tazobactam (Zerbaxa)
  - **New cephalosporin plus an older β-lactamase inhibitor**
  - **Adult dosing: 1.5 g every 8 h by IV infusion over 1 h**
  - **Two randomized phase III trials, per clinical indication, combined for approval**
    - **Complicated urinary tract infections including pyelonephritis**
    - **Complicated intra-abdominal infections used in combination with metronidazole**
- Ceftazidime-Avibactam (Avycaz)
  - **Older cephalosporin plus a new β-lactamase inhibitor**
  - **Adult dosing: 2.5 g every 8 h by IV infusion over 2 h**
  - **Initially approved on phase II data followed by phase III trial results**
    - **Complicated urinary tract infections including pyelonephritis**
    - **Complicated intra-abdominal infections used in combination with metronidazole**
    - **Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia**
- Meropenem-Vaborbactam (Vabomere)
  - **Older carbapenem plus a new β-lactamase inhibitor**
  - **Adult Dosing: 4 g every 8 h by IV infusion over 3 h**
  - **One randomized phase III trial**
    - **Complicated urinary tract infections including pyelonephritis**

Meropenem–Vaborbactam

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

Primary Study End Point	Percent Successfully Treated (n/N)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
US Food and Drug Administration			
EOIVT – mMITT Analysis[a]	98.4% (189/192)	94.0% (171/182)	4.5 (0.7 to 9.1)
European Medicines Agency[b]			
mMITT Analysis	66.7% (128/192)	57.7% (105/182)	9.0 (-0.9 to 18.7)
Microbiologic Evaluable Analysis	66.3% (118/178)	60.4% (102/169)	5.9 (-4.2 to 16.0)

[a] EOIVT, end of IV treatment (overall success in patients with clinical cure or improvement and microbial eradication)
[b] Microbial eradication at test of cure
mMITT, Microbiological modified intent-to-treat

Kaye KS, et al. *JAMA*. 2018;319:788-799.

Meropenem–Vaborbactam (TANGO 1 continued)

Secondary Study End Point	Percent Successfully Treated (n/N)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure	74.5% (143/192)	70.3% (128/182)	4.1 (-4.9 to 9.1)
Overall success at EOIVT[a]			
Acute pyelonephritis	97.5% (117/120)	94.1% (95/101)	3.4 (-2.0 to 10.2)
cUTI, removable infection source	100% (35/35)	92.1% (35/38)	7.9 (-2.5 to 20.9)
cUTI, nonremovable infection source	100% (37/37)	95.3% (41/43)	4.7 (-5.1 to 15.6)
Clinical cure at EOIVT	98.4% (189/192)	95.6% (174/182)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	90.6% (174/192)	86.3% (157/182)	4.4 (-2.2 to 11.1)
Microbial Eradication at EOIVT[b]	97.6% (188/192)	92.3% (168/182)	5.6 (1.4 to 10.7)
Microbial Eradication at test of cure[b]	68.8% (132/192)	62.1% (113/182)	6.7 (-3.0 to 16.2)

[a] EOIVT, end of IV treatment (overall success in patients with clinical cure or improvement and microbial eradication)
[b] FDA Criteria

Kaye KS, et al. *JAMA*. 2018;319:788-799.

Complicated Urinary Tract Infections, including Acute Pyelonephritis

m-MITT Population	EOIVT		Eradication Rate at TOC	
	Ceftolozane-Tazobactam	Levofloxacin	Ceftolozane-Tazobactam	Levofloxacin
Composite Cure Rates (n=800)	76.9%	68.4%	83.3%	75.4%
No Levofloxacin Resistance (n=588)	82.6%	79.7%		
Levofloxacin Resistance (n=212)	60.0%	39.3%		
	Ceftazidime-Avibactam	Doripenem	Ceftazidime-Avibactam	Doripenem
Composite Cure Rates (n=810)	70.2%	66.2%	77.4%	71.0%
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	Meropenem-Vaborbactam	Piperacillin-Tazobactam
Composite Cure Rates (n=366)	98.4%	94.3%	76.5%	73.2%

Zerbaxa® Prescribing Information, October 2016.
Avycaz® Prescribing Information, January 2017.
Vabomere™ Prescribing Information, August 2017.

m-MITT, Microbiological modified intent-to-treat
EOIVT, Overall success at end of IV treatment
TOC, Test of cure

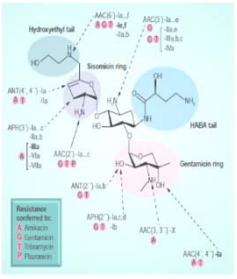
Complicated Urinary Tract Infections, including Acute Pyelonephritis

Ceftolozane-Tazobactam	Ceftazidime-Avibactam	Meropenem-Vaborbactam
Escherichia coli	*Escherichia coli*	*Escherichia coli*
Klebsiella pneumoniae	*Klebsiella pneumoniae*	*Klebsiella pneumoniae*
Proteus mirabilis	*Proteus mirabilis*	*Enterobacter cloacae* species complex
Pseudomonas aeruginosa	*Pseudomonas aeruginosa*	
	Citrobacter freundii complex	
	Enterobacter cloacae	

Zerbaxa® Prescribing Information, October 2016.
Ayvcaz® Prescribing Information, January 2017.
Vabomere™ Prescribing Information, August 2017.

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

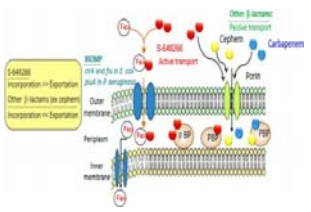
- ***A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem Followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection, including Acute Pyelonephritis, in Adults*** (NCT02486627, ClinicalTrials.gov)

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.

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 MDR *P. aeruginosa*, *A. baumannii*, *and Stenotrophomonas maltophilia* strains**



Ito-Horiyama T, et al. *Antimicrob Agents Chemother.* 2016;60:4384-6.
Kohira N, 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)
Clinical Response	89.7% (226/252)	87.4% (104/119)	2.39% (-4.66, 9.44)

  - **2:1 randomization: cefiderocol 2 grams q8h vs imipenem-cilastatin 1 gram q8h × 7–14 days**
  - **No oral step-down antibiotics**
  - **Near equal distribution of male and female subjects**
  - **More cUTI (~72%) vs acute pyelonephritis (~28%)**

Presented at the 27th ECCMID, Vienna, Austria 2017; abstract OS0250D.
Presented at IDWeek 2017, San Diego, CA 2017; abstract 1969.
Falagas ME, et al. *Expert Rev Anti Infect Ther.* 2016;14:747-63.

Intravenous Fosfomycin (Zolyd™)

- **Completed Trial (top-line results)** (NCT02753946; ClinicalTrials.gov)
  - ***Randomized, Double-Blind, Comparative Study to Evaluate the Safety and Efficacy of Intravenous Fosfomycin (ZTI-01) vs Piperacillin-Tazobactam in the Treatment of Complicated Urinary Tract Infections or Acute Pyelonephritis in Hospitalized Adults (ZEUS)***

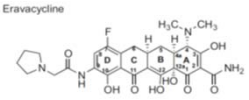
Outcome	Fosfomycin	Piperacillin-Tazobactam	Difference (95% CI)
Clinical Cure plus Microbiological Eradication	64.7% (119/184)	54.5% (97/178)	10.2% (-0.4, 20.8)
Clinical Cure Rates	90.8	91.6%	

  - **465 patient were randomized to receive either 6 grams q8h of intravenous fosfomycin (18 grams total daily dose) or 4.5 grams q8h of intravenous piperacillin-tazobactam (13.5 grams total daily dose) for 7 days (14 days if with concurrent bacteremia)**
  - **Oral step-down therapy was prohibited**

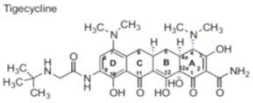
Press Release, April 5, 2017 – Zavante Therapeutics, Inc. Available at: https://www.zavante.com/zavante-therapeutics-zolyd-met-primary-endpoint-in-pivotal-zeus-study-for-treatment-of-complicated-urinary-tract-infections/.

Eravacycline: A Novel Fluorocycline

Eravacycline



Tigecycline



- **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 carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and colistin-resistant bacteria carrying *mcr-1* gene**

Zhanel GG, et al. *Drugs.* 2016; 76: 567-88.
Rodvold KA. *Kucers' The Use of Antibiotics, 7th ed.* 2018;1273-89.
Livermore DM, et al. *Antimicrob Agents Chemother.* 2016;60:3840-4.
Fyfe C, et al. *Antimicrob Agents Chemother.* 2016;60:6989-90.

Intravenous Eravacycline for cUTI

- ***A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of Eravacycline Compared With Levofloxacin in Complicated Urinary Tract Infections (IGNITE 2)***
  - **Intravenous (1.5 mg/kg q24h) to oral (200 mg q12h) transition therapy did not achieve its primary endpoint of statistical non-inferiority compared to levofloxacin 750 mg IV q24h followed by 750 mg orally q24h**
- ***A Phase 3, Randomized, Double-Blind, Double-Dummy, Multicenter, Prospective Study to Assess the Efficacy and Safety of IV Eravacycline Compared With Ertapenem in Complicated Urinary Tract Infections (IGNITE 3)***

Outcome	Eravacycline	Ertapenem	Difference (95% CI)
Micro-ITT at the EOIVT visit	84.8% (363/428)	94.8% (382/403)	-10.0 (-14.1, -6.0)
Responder Rate at the TOC visit	68.5% (293/428)	74.9% (302/403)	-6.5 (-12.6, -0.3)

m-MITT, Microbiological modified intent-to-treat
EOVIT, Overall success at end of IV treatment

Press Releases, September 8, 2015 and February 13, 2018.
Tetraphase Pharmaceutical, Inc.

Intravenous Eravacycline for cIAI

IGNITE 1 - First Phase 3, Randomized, Double-Blind Clinical Trial

Outcome	Eravacycline	Ertapenem	Difference (95% CI)
Microbiological Intent-to-Treat (micro-ITT)	86.8% (191/220)	87.6% (198/226)	-0.8 (-7.1, 5.5)
Modified Intent-to-Treat (MITT)	87.0% (235/270)	88.8% (238/268)	-1.8 (-7.4, 3.8)
Clinically Evaluable (CE)	92.9% (222/239)	94.5% (225/238)	-1.7 (-6.3, 2.8)

IGNITE 4 - Second Phase 3, Randomized, Double-Blind Clinical Trial

Outcome	Eravacycline	Meropenem	Difference (95% CI)
Microbiological Intent-to-Treat (micro-ITT)	90.8% (177/195)	91.2% (187/205)	-0.5 (-6.3, 5.3)
Modified Intent-to-Treat (MITT)	92.4% (231/250)	91.6% (228/249)	0.8 (-4.1, 5.8)
Clinically Evaluable (CE)	96.9% (218/225)	96.1% (222/231)	0.8 (-2.9, 4.5)

- **Treatment-emergent adverse event rates were similar in both treatment groups**
- **Most common drug-related adverse events for eravacycline: infusion site reactions, nausea and vomiting**
- **Adverse event profile for IV eravacycline consistent with phase 2 clinical trials in cIAI**

Solomkin JS, et al. *JAMA Surg.* 2017;152:224-32.
Horn P, et al. Presented at 28th ECCMID 2018; Abstract O-0421, Madrid, Spain.

Surgical Infection Society Revised Guidelines

Recommended Empiric Antimicrobial Regimens for Patients with Community-Acquired Intra-Abdominal Infections

Lower-Risk Patients	Higher-Risk Patients[b]
Single Agents	***Single Agents***
• Ertapenem	• Piperacillin-tazobactam
• Moxifloxacin[a]	• Imipenem-cilastatin *or* Meropenem *or* Doripenem
Combination Regimens	***Combination Regimens***
• Cefotaxime *or* ceftriaxone *plus* metronidazole	• Cefepime *plus* metronidazole
• Ciprofloxacin[a] *plus* metronidazole	• Aztreonam *plus* metronidazole *plus* vancomycin

[a] Fluoroquinolone primarily for patients with significant reactions to beta-lactam agents
[b] Ceftolozane-tazobactam or ceftazidime-avibactam plus metronidazole should be reserved for higher-risk patients with resistant pathogens and other antibiotics are not suitable

Mazuski JE, et al. *Surg Infect.* 2017;18:1-76.

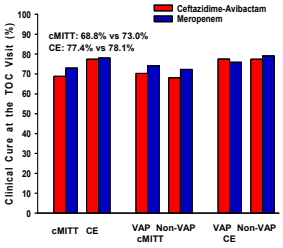
Antimicrobial Drug Development: Pathway for Gram-Negative Pathogens

Complicated Urinary Tract Infections (cUTI)	Complicated Intra-Abdominal Infections (cIAI)	Hospital-Acquired Bacterial Pneumonia (HABP)
Ceftolozane-Tazobactam*	Ceftolozane-Tazobactam*	Ceftazidime-Avibactam
Ceftazidime-Avibactam*	Ceftazidime-Avibactam*	Ceftolozane-Tazobactam
Meropenem-Vaborbactam*	Eravacycline*	Imipenem-Relebactam*
Plazomicin*		Cefiderocol
Cefiderocol*		
Fosfomycin (IV)*		

Agents currently approved or in Phase 3 drug development programs
Yellow box indicates that agent has FDA-approval for listed body site of infection
* Primary approval for entry into the US market

Nosocomial Pneumonia including VAP

Phase 3, Randomized, Multicenter Study (REPROVE Study)



Secondary Efficacy Endpoints

Per Pathogen Clinical Cure Rates and Favorable Microbiological Response at TOC	Ceftazidime-Avibactam	Meropenem
Clinical Cure		
K. pneumoniae	83.8% (31/37)	79.6% (39/49)
P. aeruginosa	64.3% (27/42)	77.1% (27/35)
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 microbiologically evaluable population

Torres A, et al. *Lancet Infect Dis.* 2018;18:285-295.

Ceftolozane-Tazobactam

- **Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia** (NCT02070757)
  - ***Increased dose***: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h
  - Treatment duration of 8 days; exception being 14 days for *Pseudomonas aeruginosa*
- **Initial report on treating respiratory infections caused by 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) Piperacillin-Tazobactam (<16) **Ciprofloxacin (>2)** Tobramycin (<2)
63 y; male	Meropenem, Ciprofloxacin	Cure / Eradication	Ceftolozane-Tazobactam (1) **Meropenem (>8)** **Cefepime (>16)** Colistin (susceptible) **Ciprofloxacin (>2)** **Tobramycin (>8)** Polymyxin (susceptible) **Piperacillin-Tazobactam (>64)**
52 y; male	Meropenem, Linezolid	Cure / Eradication	Ceftolozane-Tazobactam (1) **Meropenem (>8)** Cefepime (16) Tobramycin (<2) **Piperacillin-Tazobactam (>16)** Ciprofloxacin (<0.5)

Gelfand MS, Cleveland KO. *Clin Infect Dis.* 2015;61:853-855 [letter to editor].

"Real World" Treatment Reports

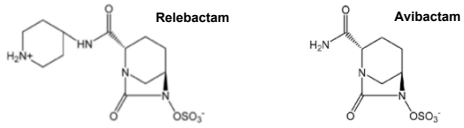
Ceftolozane-Tazobactam for MDR *Pseudomonas aeruginosa*

- **15 patient 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 *Pseudomonas 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;65:158-61.
[3] Caston JJ, et al. *Antimicrob Agents Chemother.* 2017;61(3):e02136-16.

Relebactam – A New Beta-Lactamase Inhibitor

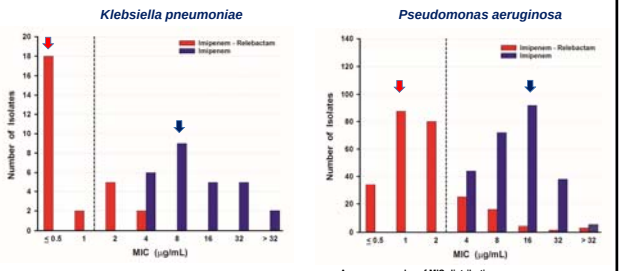
- **Relebactam (MK-7655)**
  - **Diazebicyclooctanone, non-beta-lactam, beta-lactamase inhibitor**
  - **Spectrum of activity**
    - **Potent inhibitory activity against Class A and C beta-lactamases**
    - **Not active against bacteria that produce metallo-beta-lactamases**
  - **Similar chemical structure as avibactam**



Falagas ME, et al. *Expert Rev Anti-Infect Ther.* 2016;14:747-763.
Papp-Wallace KM, Bonomo RA. *Infect Dis Clin North Am.* 2016;30:441-464.
Wong D, van Duin D. *Drugs.* 2017;77:615-628.

Imipenem-Nonsusceptible Isolates

SMART Global Surveillance Program – United States in 2015



Lob SH, et al. *Antimicrob Agents Chemother.* 2017;61:e02209-16.

Arrows are modes of MIC distributions
Dashed line CLSI susceptibility breakpoint of ≤ 1 and 2 µg/mL

Imipenem + Cilastatin – Relebactam

- ***Imipenem + Cilastatin - Relebactam versus Piperacillin-Tazobactam for Treatment of Participants with Bacterial Pneumonia (RESTORE-IMI 2)***
  (NCT02493764; clinicaltrials.gov)
  - **Double-blind, randomized study in adults (≥18 years) being treated for HABP or VABP**
    - **Imipenem-Relebactam 500 mg / 250 mg q6h vs Piperacillin-Tazobactam 4.0 g / 0.5 g every 6 hours**
    - **Concurrent linezolid IV therapy (600 mg BID) as empirical MRSA therapy**
    - **Primary Endpoint: Day 28 All-Cause Mortality**
- **Phase 2 complicated urinary tract infections trial (*n*=302 randomized patients):**
  - **1:1:1 ratio of imipenem plus relebactam 250 mg, 125 mg, placebo with switch therapy to oral ciprofloxacin after 96 hours of IV study therapy**
  - **Microbiological response: 95.5%, 98.6%, 98.7% (at end of IV therapy, *n*=230)**
  - **Composite response: 54.1%, 59.8%, 61.7% (at early follow-up [exploratory endpoint])**
- **Phase 2 complicated intraabdominal infections trial (*n*=351 randomized patients):**
  - **1:1:1 ratio of imipenem plus relebactam 250 mg, 125 mg, placebo**
  - **Clinical response: 93.7%, 95.3%, 94.9% (microbiologically evaluable, *n*=230)**

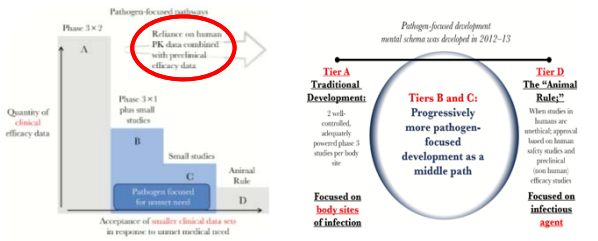
Lucasti C, et al. *Antimicrob Agents Chemother.* 2016;60:6234-6243.
Sims M, et al. *J Antimicrob Chemother.* 2017;72:2616-2626.
Falagas ME, et al. *Expert Rev Anti-Infect Ther.* 2016;14:747-763.

Cefiderocol (S-649266)

- **Ongoing Trial:**
  - ***A Multicenter, Randomized, Double-blind, Parallel-group, Clinical Study of Cefiderocol Compared with Meropenem for the Treatment of Hospital-Acquired Bacterial Pneumonia, Ventilator-Associated Bacterial Pneumonia or Healthcare-Associated Bacterial Pneumonia Caused by Gram-negative Pathogens*** (NCT03032380; ClinicalTrials.gov)
    - **Cefiderocol 2 grams q8h by IV infusion over 3 hours vs Meropenem 2 grams q8h ✕ 7–14 days**
    - **Concurrent linezolid IV therapy (600 mg q12h) as empirical MRSA therapy for at least 5 days**
    - **Primary Endpoint: All-Cause Mortality at Day 14**

Falagas ME, et al. *Expert Rev Anti Infect Ther.* 2016;14:747-63.

"Pathogen-Focused" Antibiotic Development for Resistant Gram-Negative Pathogens



Boucher HW, et al. *J Infect Dis*. 2017;216:228-236.
Rex JH, et al. *Lancet Infect Dis*. 2013;13:269-75.

Meropenem-Vaborbactam Treatment of CRE

- ***Efficacy, Safety, Tolerability of Meropenem-Vaborbactam Compared to Best Available Therapy (BAT) in Serious Infections Due to Carbapenem-Resistant Enterobacteriaceae in Adults (TANGO 2)*** (NCT02168946; clinicaltrials.gov)
  - Meropenem-Vaborbactam monotherapy (2 grams / 2 grams q8h, 3-h infusion)
  - BAT: alone or combinations of carbapenems, aminoglycosides, polymyxin B, colistin, tigecycline or ceftazidime-avibactam (monotherapy only)
  - Treatment of patients with bloodstream infection, hospital-acquired or ventilator-associated bacterial pneumonia, complicated urinary tract infection, acute pyelonephritis, or complicated intra-abdominal infections due to suspected or known CRE

Time Point	Meropenem-Vaborbactam	BAT	Difference (95% CI)
EOT: mCRE – MITT	64.3% (18/28)	40.0% (6/15)	24.3% (-6.2 to 54.8)
TOC: mCRE – MITT	57.1% (16/28)	26.7% (4/15)	30.5% (1.6% to 59.4%)
EOT: m-MITT	67.7% (21/31)	42.1% (8/19)	25.6% (-2.0% to 53.3%)
TOC: m-MITT	58.0% (18/31)	31.6% (6.19)	26.5% (-0.7 to 53.7)

EOT, end of treatment; TOC, Test of cure at 7 days after EOT
m-MITT, Microbiological modified intent-to-treat

Kaye K, et al. Presented at IDWeek 2017, San Diego, CA; abstract 1862.

Ceftazidime-Avibactam Treatment of CRE

Case series and cohort studies with outcome information due to carbapenem-resistant Enterobacteriaceae (CRE) treated with ceftazidime-avibactam (C/A)

Reference	% *Klebsiella pneumoniae*	# Treated with C/A (in Combination)	Mortality	Clinical Cure
Caston - 2017	~85% (40% KPC; 60% OXA-48)	8 (100%)	25% *vs* 52.2%	75% *vs* 34.8%
Shields - 2017	100% (97% KPC)	13 (38.5%)	7.6% *vs* 31.2%	85% *vs* 40.6%
Van Duin - 2018	97% (96% KPC)	38 (63%)	8% *vs* 32%	64% (C/A only)
Shields - 2016	84% (78% KPC)	37 (30%)	24.3%	62%
Krapp - 2017	100% (100% KPC)	6 (68.6%)	50%	66.6%
Temkin - 2017	100% (66% KPC; 34% OXA-48)	38 (65.8%)	39.5–71.4%	73.7%
King - 2017	83%	60 (55%)	32–56%	65%

Adapted from Rodriguez-Bano J, et al. *Clin Microbiol Rev*. 2018;31:e00079-17.

Carbapenem-Resistant Enterobacteriaceae
Recommended Regimens for Treatment of Infections

Risk Level, Isolate Susceptibility	Backbone Agent	Accompany Agent(s)
Low Risk[a], Monotherapy (according to susceptibility)	Ceftazidime-Avibactam, Meropenem-Vaborbactam, Meropenem, Ceftazidime, Aztreonam, Colistin, Tigecycline *or* Aminoglycoside	If intermediate susceptibility, choose another option or use combination
High Risk[a], Combination Therapy, Susceptible to a Beta-Lactam (use according to susceptibility)	Ceftazidime-Avibactam[b], Meropenem-Vaborbactam[b], Meropenem (MIC ≤8 mg/L), Ceftazidime *or* Aztreonam	Colistin, Tigecycline, Aminoglycoside *or* Fosfomycin

[a] INCREMENT Mortality Score: Low Risk < 8 points; High Risk ≥ 8 points
[b] No data about need for combination therapy when used as backbone agent. Consider source of infection in selection of agents

Rodriguez-Bano J, et al. *Clin Microbiol Rev*. 2018;31:e00079-17.

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 *Klebsiella 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:e00537-17.
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:e01369-16.
6. Spellberg B, Bonomo RA. *Clin Infect Dis*. 2016;63:1619-21.

Carbapenem-Resistant Enterobacteriaceae
High Risk, Combination Therapy (continued)

Risk Level, Isolate Susceptibility	Backbone Agent	Accompany Agent(s)
Resistant to all beta-lactams; Susceptible to at least 2 agents, including colistin	Colistin	Tigecycline, Aminoglycoside *or* Fosfomycin
Resistant to all beta-lactams and colistin; Susceptible to at least 2 agents	Tigecycline *or* Aminoglycoside	Tigecycline *or* Aminoglycoside, Fosfomycin
Pandrug-resistant or susceptible to only one agent	Meropenem plus Ertapenem, *or* Ceftazidime-Avibactam plus Aztreonam	Add any active agent; Consider investigational agent; *In vitro* testing of combinations for synergy

Rodriguez-Bano J, et al. *Clin Microbiol Rev*. 2018;31:e00079-17.

Plazomicin: Combination Treatment of CRE

- ***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**

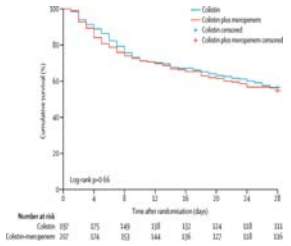
	Plazomicin	Colistin	Difference (90% exact CI)	Relative Reduction
Day 28 ACM or SDRC	23.5% (4/17)	50.0% (10/20)	26.5% (-0.7, 51.2)	53.0%
Day 28 ACM	11.8% (2/17)	40.0% (8/20)	17.25% (0.7, 52.5)	70.5%

ACM, All-cause mortality
SDRC, Significant disease related complications

Presented at the 27th ECCMID, Vienna, Austria 2017; abstract OS0250F.

Colistin Alone vs Colistin plus Meropenem
Carbapenem-Resistant Gram-Negative Bacterial Infections

- **Randomized, controlled superiority trial done in 6 hospitals in Israel, Greece, and Italy**
- **Included carbapenem-non-susceptible Gram-negative bacteria**
- **Adults with bacteremia, HABP, VABP or urosepsis**
- **1:1 randomization to IV colistin (9 MU loading dose; 4.5 MU q12h) or colistin plus meropenem (2 g prolonged infusion q8h)**
- **406 patients, most having pneumonia or bacteremia (87%) caused by *A. baumannii* (77%)**
- **Increased diarrhea and decreased incidence of mild renal failure with combination therapy**



Paul M, et al. *Lancet Infect Dis.* 2018;18:391-400.

Imipenem-Cilastatin – Relebactam
Carbapenem-Resistant Gram-Negative Bacterial Infections

- ***Efficacy and Safety of Imipenem + Cilastatin - Relebactam (MK-7655) versus Colistimethate Sodium plus Imipenem + Cilastatin in Imipenem-Resistant Bacterial Infections (RESTORE-IMI 1)*** **(NCT02452047; Clinicaltrials.gov)**
  - **Double-blind, randomized study in adults (≥18 years) being treated for cUTI, cIAI, HABP or VABP caused by IMI-resistant pathogens but IMI-Relebactam-susceptible and colistin-suscepitible**

Outcome	Imipenem-Relebactam	Imipenem + Colistin	Unadjusted Difference
Favorable Overall Response HABP/VABP cUTI cIAI	71.4% (15/21) 87.5% (7/8) 72.7% (8/11) 0% (0/2)	70.0% (7/10) 66.7% (2/3) 100% (5/5) 0% (0/2)	1.4% 20.8% -27.3% 0%
Favorable Clinical Response (Day 28)	71.4% (16/21)	40.0% (4/10)	31.4%
28-Day All-Cause Mortality	9.5% (2/21)	30.0% (3/10)	-20.5%

  - **Qualifying baseline pathogens were *Pseudomonas aeruginosa* (77%), *Klebsiella* spp. (16%), and other Enterobacteriaceae (6%)**
  - **β-lactamase detected: AmpC (84%), ESBLs (39%), KPC 16%, OXA-48 (3%)**

Motsch J, et al. Presented at the 28th ECCMID 2018; Abstract O-0427, Madrid, Spain.

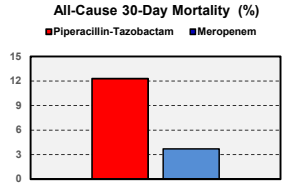
Non-Carbapenem Beta-Lactams
Treatment of ESBL Infections

- 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;64:972-980.

MERINO TRIAL
Piperacillin-Tazobactam vs Meropenem

- **Definitive treatment of bloodstream infections (BSIs) caused by 3rd-generation cephalosporin non-susceptible *E. coli* and *Klebsiella* spp.**
- **February 2014 to July 2017**
- **379 patients randomized appropriately**
- **Piperacillin-tazobactam 4.5 g q6h (*n* = 187) vs meropenem 1 g q8h (*n* = 191)**
- **BSIs were most frequently healthcare-associated (56.4%)**
- **60.9% urinary tract origin; *E. coli* (86.6%)**
- **No differences in subsequent infection with carbapenem-resistant Gram-negative organisms or *C. difficile* between study arms**



12.3% vs 3.7%
Risk Difference: 8.6% (95% CI: 3.4%, 14.5%)
RR: 3.4, 95% CI 1.5 to 7.6; p = 0.002

Harris P, et al. Presented at the 28th ECCMID 2018; Abstract O-01121, Madrid, Spain.

New Antimicrobial Agents Being Developed to Treat Resistant Gram-Negative Bacteria

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

BLBLI, Beta-lactam-beta-lactamase inhibitors combinations