Activity Description

Target Audience

This continuing pharmacy education activity meets the needs of pharmacists in a variety of practice settings, including large and small healthcare systems, outpatient clinics, managed care organizations, long-term care facilities, and academia. This program targets pharmacists who are at the forefront of caring for patients with serious bacterial infections.

Learning Objectives

Upon completing this activity, participants will be able to:

- Explain the impact of local epidemiological trends and resistance mechanisms of Gram-negative bacteria on initial antimicrobial selection
- Evaluate the potential role of newer and novel antimicrobial agents in targeting antimicrobial-resistant Gram-negative pathogens
- Apply antimicrobial stewardship strategies to improve appropriate use of antimicrobials
- Utilize collaborative care model to improve patient outcomes during the pandemic era

Faculty

James S. Lewis II, PharmD, FIDSA
ID Pharmacy Supervisor and Associate Professor
Oregon Health and Science University
Departments of Pharmacy and Infectious Diseases
Portland, OR

James S. Lewis, PharmD has relevant financial relationships with ineligible companies to disclose:
Consultant: Merck & Co., Selux Diagnostics, Cidara
Dr. Lewis intends to discuss the off-label use of the following: Uses of FDA approved antibacterials for infections due to resistant organisms that may not be within the current FDA list of indications.

No (other) speakers, authors, planners or content reviewers have any relevant financial relationships to disclose. Content review confirmed that the content was developed in a fair, balanced manner free from commercial bias. Disclosure of a relationship is not intended to suggest or condone commercial bias in any presentation, but it is made to provide participants with information that might be of potential importance to their evaluation of a presentation.

What do the HAP/VAP Guidelines Say? – Microbiology & Stewardship

1. We recommend that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is specific to their intensive care population(s) if possible.

Kalil AC, et al. *Clin Infect Dis.* 2016;63:575-82.

What Your Antibiogram Does (and Doesn't) Tell You

- Empiric therapy
- Hospital-wide data
- First isolate per patient per year
- The importance of unit-specific data
- The importance of site-specific data

Ways to Think About Your Antibiogram – The New CLSI M39 – Coming Soon!

- Tips and tricks for antibiogram preparation
- Combining results from rapid diagnostics and resistance marker testing with the antibiogram
- Antibiograms for multiple facilities & long-term care facilities
- How stewardship programs can use antibiogram data
- "^" with intermediate breakpoints & agents that concentrate in the urine

… And Much More!!

CLSI. M39. Available at: https://clsi.org/standards/products/microbiology/documents/m39/.

Things to Think About With Your Antibiogram: Are Blood Isolates a Good Proxy for Other Infections?

- Short answer – NO!
- Resistance among respiratory isolates is more common
- Particularly in ICU patients
- Especially true for *P. aeruginosa* (PA) and *S. pneumoniae* (SP)
- Enterobacterales: a difference still exists but less than for PA and SP

Horner C, et al. *J Antimicrob Chemother*. 2021;76:1822-31.

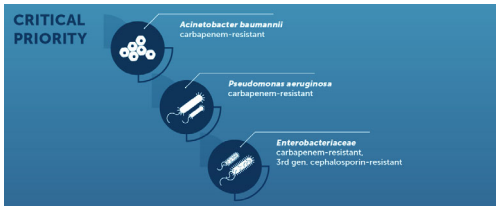
CDC: Drug-Resistant Gram-Negative Bacterial Infection Threats

Urgent and Serious

Urgent	Carbapenem-resistant Enterobacteriaceae (CRE) Carbapenem-resistant *Acinetobacter*
Serious	ESBL-producing Enterobacteriaceae Multidrug-resistant *Pseudomonas aeruginosa*

CDC. Antibiotic Resistance Threats in the United States, 2019. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

WHO Priority Pathogens List For R&D of New Antibiotics



*Enterobacteriaceae include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.

WHO. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. Available at: https://https://www.who.int/publications/i/item/9789240021303.

World Health Organization

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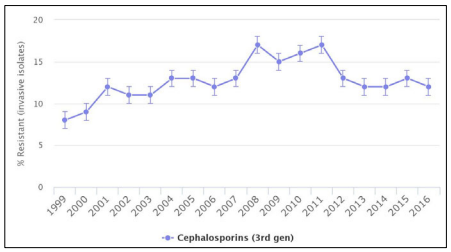
2020 antibacterial agents in clinical and preclinical development: an overview and analysis

15 April 2021 | Technical document

"Overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance."

WHO. 2020 antibacterial agents in clinical and preclinical development: an overview and analysis. Available at: https://https://www.who.int/publications/i/item/9789240021303.

Prevalence of ESBL-producing *K. pneumoniae* in the US



Center for Disease Dynamics, Economics & Policy. Resistance Map. https://resistancemap.cddep.org/AntibioticResistance.php.

American Society for Microbiology | Journal of Clinical Microbiology®

EPIDEMIOLOGY

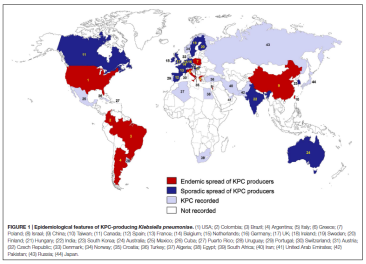
Prevalence of bla_{CTX-M} Genes in Gram-Negative Bloodstream Isolates across 66 Hospitals in the United States

Pranita D. Tamma,[a] Tiffeny T. Smith,[b] Ayomikun Adebayo,[c] Sara M. Karaba,[d] Emily Jacobs,[c] Teresa Wakefield,[c] Kelly Nguyen,[b] Natalie N. Whitfield,[b] Patricia J. Simner[c]

- *E. coli* – the bigger ESBL problem?
- *E. coli* - 49% of bloodstream Gram(-) isolates
- 16% contained bla_{CTX-M} – not the entire story

Tamma PD, et al. *J Clin Microbiol*. 2021;59:e00127-21. DOI: https://doi.org/10.1128/JCM.00127-21.

World-wide Spread of KPC-producing *K. pneumoniae*



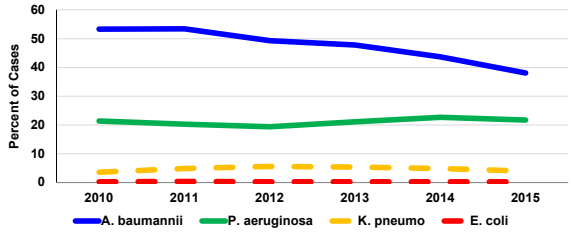
Lee C-R, et al. *Front Microbiol.* 2016;7:895.

Molecular Landscape of Carbapenemase-Producing *Acinetobacter baumannii* (CRAB) in the US

- 8/2017 – 7/2019: 2,368 CRAB isolates from 44 states
- 12 (0.5%) harbored KPC or metallo-beta-lactamase enzymes
- Class D β-lactamases of the OXA type are common in CRAB
- Limited options for group D enzymes
- Limited activity of current BL/BLI combinations & questions with cefiderocol

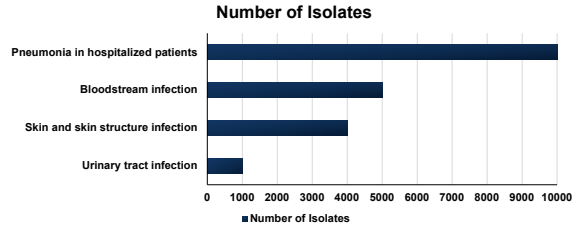
Burrell K, et al. *Infect Control Hosp Epidemiol.* 2020;46(S1):s320-21. DOI: https://doi.org/10.1017/ice.2020.917.

Percentage of Total Carbapenem-Resistant Cases Contributed By Pathogen



Cai B, et al. *Open Forum Infect Dis.* 2017;4: DOI: 10.1093/ofid/ofx176.

Distribution of *P. aeruginosa* Isolates by Infection Type – North America (SENTRY 1997–2016)



Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:s63-8.

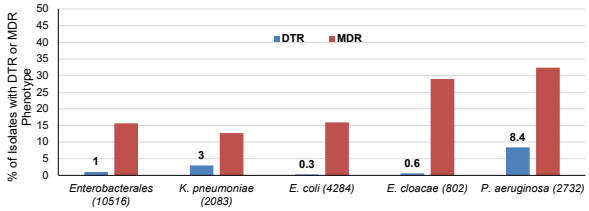
Susceptibility of *P. aeruginosa* From U.S. ICU Patients With Bloodstream Infections or Pneumonia

	MIC_{90}, mg/L	% Susceptible
Aztreonam	>16	66.5
Cefepime	16	83.8
Ceftazidime	32	82.0
Ciprofloxacin	>4	73.9
Meropenem	8	76.3
Piperacillin-tazobactam	>64	77.1

Amikacin, gentamicin, and colistin look better – 98%, 87%, 99.4% - excited to use them?

Shortridge D, et al. *Open Forum Infect Dis.* 2019;6:ofz240.

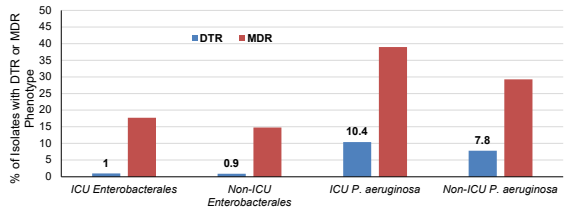
U.S. Resistance Data: 2015–2017



DTR = Not susceptible to all tested beta-lactams and fluoroquinolones
MDR = Not susceptible to at least 1 agent in 3 or more classes of antibiotics

Karlowsky JA, et al. *Clin Infect Dis.* 2021;72:2112.

Non-ICU vs ICU Resistance Rates



DTR = Not susceptible to all tested beta-lactams and fluoroquinolones
MDR = Not susceptible to at least 1 agent in 3 or more classes of antibiotics

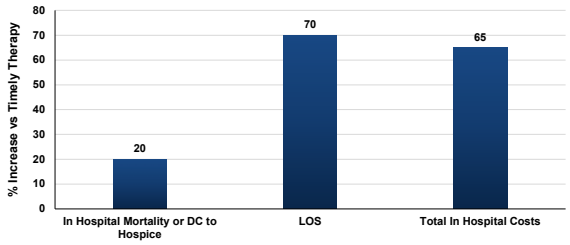
Karlowsky JA, et al. *Clin Infect Dis*. 2021;72:2112.

Combination Therapy with Colistin or Aminoglycosides vs Ceftolazane/Tazo for Drug-Resistant *P. aeruginosa*

- **Clinical Cure:**
  - Ceftol/Tazo = 81%
  - Polymyxins = 66% (p=0.05)
  - Aminoglycosides = 55% (p=0.002)
- **Acute Kidney Injury**
  - Ceftol/Tazo = 6%
  - Polymyxins = 43% (p=0.0001)
  - Aminoglycosides = 23% (p=0.007)
- **Pneumonia outcomes (p=0.02)**
  - 80% success ceftol/tazo
  - 56% polymyxin or aminoglycoside

Pogue JM, et al. *Clin Infect Dis*. 2020;71:304-310.

Impact of Delayed Appropriate Therapy on Clinical and Economic Outcomes: Resistant or Susceptible Organisms



Bonine NG, et al. *Am J Med Sci*. 2019;357:103-110.

Ceftolozane-Tazobactam for Ventilated Nosocomial Pneumonia

- In patients with positive baseline LRT cultures
  - (70%) causative Gram-negative pathogens
  - Enterobacteriaceae (74%)
  - *P. aeruginosa* (25%)
- Importance of knowing your local antibiogram for these organisms
- Importance of knowing the risk factors for MDR pathogens
- Importance of optimizing PK/PD for bacterial pneumonia

Kollef MH, et al. *Lancet Infect Dis*. 2019;19:1299-1311.

Gram-negative Organisms in Recent Trials

	REPROVE[1] (n = 264)	ASPECT-NP[2] (n = 499)	RESTORE-IMI 2[3] (n = 364)
P. aeruginosa	77 (29%)	128 (26%)	85 (23%)
Enterobacterales	197 (75%)	380 (76%)	212 (58%)
K. pneumoniae	86 (33%)	177 (35%)	111 (30%)
E. coli	29 (11%)	93 (19%)	67 (18%)
E. cloacae	32 (12%)	33 (7%)	27 (7%)
P. mirabilis	19 (7%)	44 (9%)	NR
S. marcescens	20 (7%)	30 (6%)	17 (5%)
E. aerogenes	11 (4%)	NR	NR
K. oxytoca	NR	26 (5%)	NR
H. influenzae	24 (9%)	38 (8%)	26 (7%)
A. baumannii	NR	38 (8%)	69 (19%)

1. Torres A, et al. *Lancet Infect Dis*. 2018;18:285-295. 2. Kollef MH, et al. *Lancet Infect Dis*. 2019;19:1299-1311.
3. Titov I, et al. *Clin Infect Dis*. 2020;ciaa803, https://doi.org/10.1093/cid/ciaa803.

Rapid Diagnostics to Hasten Pathogen Identification and Susceptibility

Technology	Examples	Pathogen/Resistance Detection	Turnaround Time	Clinical Considerations
Real time PCR	Xpert® MRSA/SA BC	MRSA, MSSA, mec A/C	≤ 2 hr	• Prompt differentiation between MRSA and MSSA
	BD Max™ MRSA Staph SR/XT	MRSA, MSSA, mec A/C	≤ 2 hr	
Multiplex PCR	Biofire Filmarray® BC	GBP, GNB, *Candida* spp., mecA, vanA/B, KPC	≤ 2 hr	• Comprehensive number of targets • Not Gram-stain dependent
	Verigene® BC-GP	GPB, mecA, vanA/B	2.5 hr	
	Verigene® BC-GN	GNB, CTX-M, IMP, KPC, NDM, OXA, VIM	2 hr	
	Curetis Unyuero™ BCU	GPB, GNB, fungal panel, mycobacteria, 16 resistance genes	4 hr	
	Icubate IC GPC	GPC, mec A, vanA, vanB	4-5hr	• Many false negatives for *S. pneumoniae*
MALDI-TOF MS	bioMérieux VITEK® MS	Database for bacteria, fungi, mycobacteria, molds	<2 hr	• Detect many potential pathogens • Able to detect limited resistance mechanisms
	Bruker Sepsityper®		<2 hr	
PNA-FISH	AdvanDx QuickFISH®	GPB, GNB, *Candida* spp.	<2 hr	• Limited target detection • Rapid phenotypic AST

Guillamet MCV, et al. *Semin Respir Crit Care Med*. 2019;40:454-464.

Availability of Susceptibility Testing

Antimicrobial	Disk Diffusion	Gradient Diffusion		Other	
		Liofilchem	E-Test	Sensititre Tray	Automated Systems
Ceftazidime-avibactam	Yes	Yes	Yes	Yes	Microscan Vitek-2
Ceftolozane-tazobactam	Yes	Yes	Yes	Yes	Microscan Vitek-2
Eravacycline	Yes	Yes	Yes	Yes	No
Meropenem-vaborbactam	Yes	Yes	Yes	Yes	BD Phoenix
Omadacycline	Yes	Yes	No	Yes	No
Plazomicin	Yes	Yes	Yes	Yes	No
Imipenem-Relebactam	Yes	Yes	Yes	Yes	No
Cefiderocol	Yes	Yes	No	Yes	No

Original Slide Courtesy of Kristi Traugott, PharmD. – Updated 7-2021.

What do the Guidelines Say?

Values and preferences: These recommendations place a high value on targeting the specific pathogens associated with VAP as narrowly as possible to assure adequate treatment while minimizing overtreatment and its undesirable consequences.

Kalil AC, et al. *Clin Infect Dis.* 2016;63:575-82.

What do the Guidelines Say? Stewardship & Empiric Antibiotic Selection

Table 2. Risk Factors for Multidrug-Resistant Pathogens
Risk factors for MDR VAP
Prior intravenous antibiotic use within 90d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90d
Risk factors for MRSA HAP/VAP
Prior intravenous antibiotic use within 90d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90d

Kalil AC, et al. *Clin Infect Dis.* 2016;63:575-82.

Empiric Treatment Options for Clinically Suspected VAP Where Empiric MRSA Coverage & Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

Gram-positive MRSA Antibiotic	Gram-negative Antibiotic With Antipseudomonal Activity: β-Lactam-Based Agents	Gram-negative Antibiotic With Antipseudomonal Activity: Non-β-Lactam-Based Agents
Vancomycin 15mg/kg IV q8-12h	Piperacillin-tazobactam 4.5g IV Q6h	Ciprofloxacin 400mg IV Q8h
		Levofloxacin 750mg IV Q24h
OR	OR	OR
Linezolid 600mg IV Q12h	Cefepime 2g IV Q8h	Amikacin 15-20mg/kg IV q24h
	Ceftazidime 2g IV Q8h	Gentamicin 5-7mg/kg IV Q24h
		Tobramycin 5-7mg/kg IV Q24h
	OR	OR
	Imipenem 500mg IV q6h	Colistin 2.5mg IV Q12h (after load)
	Meropenem 1g IV q8h	Polymyxin B 1.25-1.5mg/kg IVQ12h

Kalil AC, et al. *Clin Infect Dis.* 2016;63:575-82.

RESEARCH Open Access

Intrapulmonary concentrations of meropenem administered by continuous infusion in critically ill patients with nosocomial pneumonia: a randomized pharmacokinetic trial

- Failed prior NP trials (e.g., tigecycline) guide the use of max doses in more recent trials (e.g., ceftolozane)
- Lung penetration studies demonstrate a need to optimize PK/PD
- These data suggest that for "susceptible" bugs (MIC <4 mg/L), meropenem at 2 g Q8h is required

Benitez-Cano A, et al. *Crit Care.* 2020;24:55.

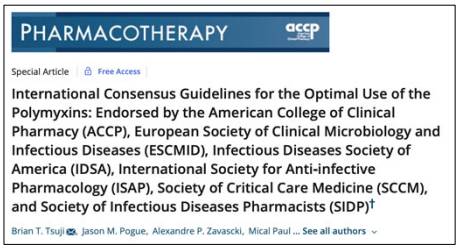
What's Missing, What's New, & What's an Option?

- Ceftolozane-Tazobactam: FDA-approved pneumonia indication
- Ceftazidime-Avibactam: FDA-approved pneumonia indication
- Meropenem-Vaborbactam: Not active for Mero-R *P. aeruginosa*
- Imipenem-Relebactam – FDA-approved pneumonia indication
- Cefiderocol – FDA-approved pneumonia indication

What's Missing, What's New, & What's an Option?

- **Plazomicin:**
  - Variable *P. aeruginosa* activity
  - <<potent than tobramycin
  - Issues with aminoglycosides in pneumonia
- **Eravacycline:**
  - No *P. aeruginosa* activity, no pneumonia data
  - MDR *Acinetobacter* spp.?
  - Metallo-beta-lactamase stability
- **Delafloxacin:**
  - No advantage over levofloxacin or ciprofloxacin for *P. aeruginosa*
  - Comparable to levofloxacin and ciprofloxacin for other GNRs

New Consensus Guidelines for the Optimal Use of Polymyxins


PHARMACOTHERAPY accp

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International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Brian T. Tsuji, Jason M. Pogue, Alexandre P. Zavascki, Mical Paul ... See all authors

Tsuji, BT, et al. *Pharmacotherapy*. 2019;39:10-39.

New CLSI Colistin/Polymyxin B Comments

- Clinical and PK/PD data suggest that this agent is of limited clinical efficacy, even if a susceptible result is obtained.
- If available, alternative non-polymyxin agents are strongly preferred. If these agents are not available, this breakpoint presumes use of colistin in combination with one or more additional, active antimicrobials.
- Colistin (methanesulfonate) should be given with a loading dose and maximum renally-adjusted doses.
- Polymyxin B should be given with a loading dose and maximum recommended doses.
- When given intravenously, this drug is unlikely to be effective for pneumonia.

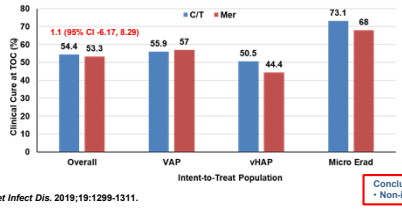
CLSI M100 30th ed. 2020.
Satlin MJ, et al. *Clin Infect Dis*. 2020;ciaa121. doi: 10.1093/cid/ciaa121.

What Do We Know About the Newer Agents in HAP/VAP?

- Ceftazidime-avibactam: FDA-approved indication
- Ceftolozane-tazobactam: FDA-approved indication
  - 3 g (HABP/VABP) vs. 1.5 g (cIAI/cUTI)
- Imipenem-Relebactam: FDA-approved indication
- Cefiderocol: FDA-approved indication
- In vitro vs clinical and struggles in HAP/VAP with new agents

Ceftolozane-Tazobactam for Nosocomial Pneumonia (ASPECT-NP)

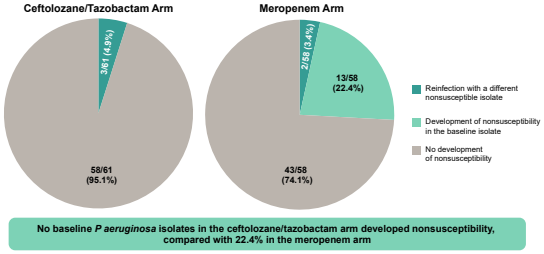
- Randomized controlled, double-blind phase III, non-inferiority trial comparing ceftolozane-tazobactam (3 g q8h) vs. meropenem (1 g q8h) for treatment of nosocomial pneumonia
  - **All patients were ventilated**



Conclusions:
- Non-inferior in all patient populations

Kollef MH, et al. *Lancet Infect Dis*. 2019;19:1299-1311.

Emergence of Nonsusceptibility Among Baseline *P. aeruginosa* Isolates (ASPECT-NP)

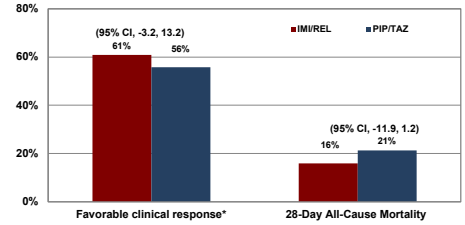


No baseline *P aeruginosa* isolates in the ceftolozane/tazobactam arm developed nonsusceptibility, compared with 22.4% in the meropenem arm

Motyl M, et al. 30th ECCMID; Paris, France; April 18–21, 2020. Poster 1215.

Imipenem-Relebactam (IMI/REL) vs. Piperacillin-Tazobactam (PIP/TAZ) for HABP/VABP (RESTORE-IMI 2)

Multicenter, randomized, DB trial comparing IMI/REL (500/250mg q6h) vs PIP/TAZ (4g/500mg q6h)



Drug-related AEs:
- 12% (31/266) IMI/REL
- 10% (26/269) PIP/TAZ

*At 7 to 14 days after completing therapy

Titov I, et al. *Clin Infect Dis*. 2020;ciaa803, https://doi.org/10.1093/cid/ciaa803.

Ceftolozane-Tazobactam & Imipenem-Relebactam for MDR *P. aeruginosa*

Cross-susceptibility of ceftolozane-tazobactam and imipenem-relebactam vs MDR *P. aeruginosa* from ICU & non-ICU wards (n=442)

		Imipenem-Relebactam		
		Susceptible	Intermediate	Resistant
Ceftolozane-Tazobactam	Susceptible	297 (67.2%)	37 (8.4%)	24 (5.4%)
	Intermediate	31 (7.0%)	6 (1.4%)	7 (1.6%)
	Resistant	21 (4.8%)	7 (1.6%)	12 (2.7%)

21/40 (52.5%) of ceftolozane-tazobactam R isolates were imipenem-relebactam susceptible

Depestel D, et al. *Crit Care Med*. 2019;47(suppl 1): Abstract 658.

Ceftazidime-Avibactam Phase 3 Trials

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow

- HABP/VABP
- cUTI
- cIAI

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

Avycaz® (ceftazidime-avibactam) Prescribing Information. Allergan USA Inc., Madison, NJ. Updated March 2019.

Ceftazidime-Avibactam HAP/VAP Trial – An Interesting Finding

- Increasing MICs (≥4× baseline) at EOT or TOC and same genotype as the baseline isolate were observed in:
  - 1 patient in ceftazidime/avibactam group – *K. pneumoniae*
  - 11 patients in meropenem group – 10 with *P. aeruginosa*
- Consistent theme with *P. aeruginosa* & carbapenems?

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

Further Evidence

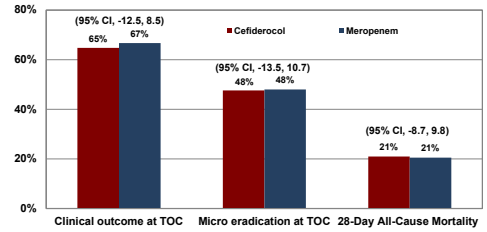
Ceftazidime vs. Carbapenems vs. Piperacillin-Tazobactam as Single Definitive Therapy for *Pseudomonas aeruginosa* Bloodstream Infection – A Multi-Site Retrospective Study

- No difference in mortality
- No difference in clinical or microbiologic failure
- Adverse events similar
- Higher rates of antipseudomonal drug-resistant *P. aeruginosa* with carbapenem use (p=0.007)

Babich T, et al. *Clin Infect Dis*. 2020;70:2270-80.

Cefiderocol (CFDC) Vs. Meropenem (MER) for Nosocomial Pneumonia (APEKS-NP)

Multicenter, randomized, DB comparing CFDC (2 g q8h) vs MER (2 g q8h) for HAP, VAP, or HCAP



Drug-related AEs:
- 9.5% (14/148) CFDC
- 11.3% (17/150) MER

Wunderink RG, et al. *Lancet Infect Dis*. 2020; DOI: https://doi.org/10.1016/S1473-3099(20)30731-3.

COVID-19 and VAP: Is it Different?

- 568 COVID-19 patients: 50.5% with VAP or VAT
- Higher rate than seen with influenza or non-viral pneumonia
- Diagnostic issues due to healthcare worker protection
- Other issues due to ICU crowding
- Commonly-seen issues in COVID patients placing them at higher risk
  - Prolonged mechanical ventilation
  - Prolonged sedation
  - Immune impairment
  - More frequent proning required
  - Higher risk of pulmonary infarction

Wicky PH, et al. *Crit Care.* 2021;25:153.

COVID-19: Bacterial Superinfection with Mechanical Ventilation

- 386 BAL samples from 179 COVID-19 patients requiring MV
- Within 48 hours of MV, bacterial superinfection detected in 21% of patients
  - 72 patients (44.4%) had ≥1 VAP episode
  - 15 cases of initial VAP caused by difficult-to-treat bacteria

Pickens CO, et al. *Am J Resp Crit Care Med.* 2021;doi: 10.1164/rccm.202106-1354OC [Online ahead of print].

Activity of New Agents vs. Problematic Organisms/Resistance Mechanisms

	CR-Pa	CR-Acineto	ESBL-Eb	KPC-Eb	Metallo-BL	OXA-48-Eb
Ceftolozane-Tazobactam	+	-	+/-	-	-	?
Ceftazidime-Avibactam	+	-	+	+	-	+
Meropenem-Vaborbactam	-	-	+	+	-	-
Imipenem-Relebactam	+	-	+	+	-	-
Cefiderocol	+	+	+	+	+	+
Piazomicin	-	-	+	+	-*	-*
Eravacycline	-	+/-	+	+/-	+/-	+/-

*Resistance due to presence of 16rRNA methyltransferases in many of these organisms

Jacobs MR, et al. *IDWeek* 2108 Poster 1348.; Livermore DM, et al. *Antimicrob Agents Chemother.* 2016;60:3840.
Stewart A, et al. *Antimicrob Agents Chemother.* 2018;62:e01195.

2020 IDSA Guidance on Treatment of Antimicrobial-Resistant Gram-negative Infections

Goal: Assist clinicians in the selection of antibiotic therapy for infections caused by ESBL-Enterobacterales, CRE, and difficult-to-treat (DTR)* *P. aeruginosa*

- Pathogens selected as they are:
  - Designated urgent or serious threats by CDC
  - Encountered in hospitals of all sizes
  - Cause a wide range of serious infections that carry significant morbidity and mortality

*DTR defined as non-susceptibility to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin
IDSA. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections, Sept. 8, 2020. Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

IDSA Guidance: ESBLs and DTR *P. aeruginosa*
(Non-Urinary Tract Infections)

Pathogen	Preferred Therapy
ESBL Enterobacterales[a]	Meropenem Imipenem-cilastatin Ertapenem
DTR *P. aeruginosa*[b]	Ceftolozane-tazobactam Ceftazidime-avibactam Imipenem-cilastatin-relebactam Alternative: cefiderocol

[a]For ESBL Enterobacterales infections, piperacillin-tazobactam and cefepime should be avoided, even if susceptibility to these agents has been demonstrated
[b]For DTR *P. aeruginosa* infections, combination therapy is not routinely recommended if in vitro susceptibility to a preferred agent is confirmed

DTR, difficult-to-treat
IDSA. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections, Sept. 8, 2020.
Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

IDSA Guidance: Treatment for CRE Infections
(Non-Urinary Tract Infections)

CRE Phenotype/Genotype	Preferred Therapy
Ertapenem resistant, Meropenem susceptible*	Meropenem (extended infusion)
Ertapenem and meropenem resistant*	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam
KPC identified (or carbapenemase positive but identity unknown)	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam
Metallo-beta-lactamase carbapenemase identified	Ceftazidime-avibactam + Aztreonam Cefiderocol
OXA-48-like carbapenemase identified	Ceftazidime-avibactam

Note: For CRE infections, polymyxin B and colistin should be avoided; combination therapy (i.e., a beta-lactam plus an aminoglycoside, fluoroquinolone, or polymyxin) is not routinely recommended.

*Carbapenemase testing results are either not available or negative
IDSA. IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-negative Infections, Sept. 8, 2020.
Available at: https://www.idsociety.org/practice-guideline/amr-guidance/.

Conclusions

- Knowing the susceptibility of the organisms you're likely to encounter in HABP/VABP is critical
- Resistance is more common in ICU settings/patients
- Susceptibility testing of newer agents can be challenging
- Colistin/Polymyxin B need to largely disappear from clinical use
- There are very important differences between new agents both in available clinical data and in vitro activity

Patient Case Scenario #1

- A 59-year-old woman is admitted to a community hospital in rural Washington state for an emergent appendectomy.
- Upon entry into the abdominal cavity, it is found that the appendix has ruptured.
- During irrigation there is also concern for an intestinal perforation and the patient is subsequently admitted to the ICU requiring prolonged sedation and prolonged intubation post operatively.
- She has no known recent antibiotic exposure and she is started on piperacillin-tazobactam.

Patient Case Scenario #1 (cont'd)

- On post-op and pip-tazo day 4, she develops fever, purulent sputum, and increased WBC to 30k/mm^3.
- Chest X-ray identifies a new pulmonary infiltrate in the right lower lobe and an ET tube aspirated sputum reveals high numbers of a neutrophils and Gram-negative rods.
- Multidrug-resistance among Gram-negative pathogens is less than 10% in the institution per the antibiogram.
- The hospital data shows that approximately 16% of Enterobacterales produce ESBLs and carbapenem resistance within *P. aeruginosa* is seen in 20% of isolates.
- No carbapenemase-producing organisms have been previously identified in this hospital.

Patient Case Scenario #1: Discussion Question

Culture and susceptibility results will be available in 48–72 hours. Which of the following would be the most appropriate initial antimicrobial agent?

A. Cefepime + metronidazole
B. Meropenem
C. Ceftolozane-tazobactam
D. Cefiderocol

Patient Case Scenario #2

- Consider a similar scenario now set in a hospital in Chicago where the rate of carbapenem resistance among Enterobacterales is 17%.
- The patient has been in the ICU for the past 17 days after being admitted for severe COVID-19.
- There has been a recent outbreak of NDM-producing *E. cloacae* in the surgical ICU on the same floor.
- Though the hospital has rapid diagnostics available, the clinical microbiology lab utilizes rapid molecular diagnostics for blood culture isolates and uses MALDI-TOF for bacterial identification.
  - Relies on a traditional automated AST system for susceptibility results.

Patient Case Scenario #2: Discussion Question

Which of the following would be the most appropriate initial antimicrobial agent?

A. Piperacillin-tazobactam
B. Imipenem-cilastatin
C. Ceftazidime-avibactam
D. Cefiderocol