Core Concepts: Antibacterial Drugs I
Approach to Resistant Gram-Negative Bacilli

Pranita D. Tamma, MD, MHS

Johns Hopkins University School of Medicine
Professor, Pediatrics

8/4/2025

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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Objectives

- Review the antibiotic treatment for infections caused by:
  - Extended-spectrum β-lactamase producing Enterobacterales (ESBL-E)
  - AmpC β-lactamase producing Enterobacterales (AmpC-E)
  - Carbapenem-resistant Enterobacterales (CRE)

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Clinical Infectious Diseases
IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

Provides guidance on the treatment of:

- Extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E)
- AmpC beta-lactamase producing Enterobacterales (AmpC-E)
- Carbapenem-resistant Enterobacterales
- *Pseudomonas aeruginosa* with difficult-to-treat resistance
- Carbapenem-resistant *Acinetobacter baumannii* complex
- *Stenotrophomonas maltophilia* infections

www.idsociety.org/practice-guideline/amr-guidance/

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ESBL-E Infections

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Clinical Case

- 18-year-old female
- Renal transplant secondary to focal segmental glomerulosclerosis
- Multiple urinary tract infections in the past including <1 month ago
- Dysuria, fevers, rigors, and hypotension
- ICU to initiate vasopressors
- Urine and blood cultures growing *Escherichia coli*

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Antibiotic	MIC	Interpretation*
Amikacin	>8 µg/mL	R
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	2 µg/mL	S
Cefepime	4 µg/mL	SDD
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin-tazobactam	8/4 µg/mL	S
Tobramycin	1 µg/mL	S
Trimethoprim-sulfamethoxazole	0.5/4 µg/mL	S

*Applying Clinical and Laboratory Standards Institute 2024 breakpoints

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Question #1

Which of the following is the preferred initial agent for a women presenting with bacteremia secondary to a urinary tract infection caused by ESBL-producing *Escherichia coli*?

A. Ceftriaxone
B. Piperacillin-tazobactam
C. Cefepime
D. Meropenem
E. Ceftazidime-avibactam

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A Primer on ESBL-E

- ESBLs are enzymes that inactivate penicillins, cephalosporins, and aztreonam
  - Do not inactivate non-β-lactam agents (e.g., aminoglycosides, TMP-SMX, ciprofloxacin, doxycycline)
- Organisms carrying ESBL genes often harbor antimicrobial resistance determinants to a broad range of antibiotics
- Most commonly produced by *Escherichia coli, Klebsiella pneumoniae*, & *Klebsiella oxytoca*
  - Less than **10%** of other Enterobacterales species produce ESBL enzymes
- Routine ESBL testing not performed by most clinical microbiology laboratories on all specimens; if performed often limited to blood isolates
  - **Ceftriaxone MICs ≥2 µg/mL** for the above species often used as a surrogate by clinicians for ESBL production (limited specificity and perhaps overly sensitive)
- CTX-M enzymes are the most common ESBLs
  - About **10-15%** of ESBL enzymes are not CTX-M enzymes

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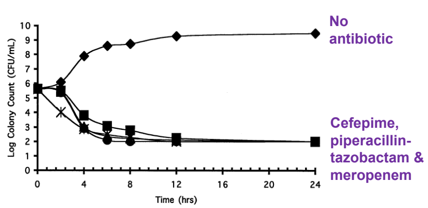
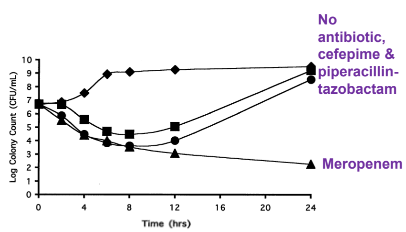
Piperacillin-Tazobactam (PTZ): Inoculum Effect

Caveat: Relevance to clinical practice?



Low inoculum ESBL growth curve



High inoculum ESBL growth curve

Burgess D, et al. Diag Microbiol Infect Dis 2004; 49:41.

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What are Some Concerns with Tazobactam as an ESBL Inhibitor?

1. Designed to inhibit SHV and TEM ESBL variants and not CTX-M ESBLs
2. Tazobactam effectiveness may be diminished with increased expression of ESBL enzymes, multiple ESBLs, or presence of other β-lactamases (e.g., OXA-1, AmpC enzymes)
   - Only 8:1 ratio of piperacillin to tazobactam compared to 2:1 ratio of ceftolozane to tazobactam
3. Piperacillin-tazobactam breakpoint for Enterobacterales exclusively based on pharmacokinetic-pharmacodynamic considerations of piperacillin and not tazobactam

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JAMA

Research

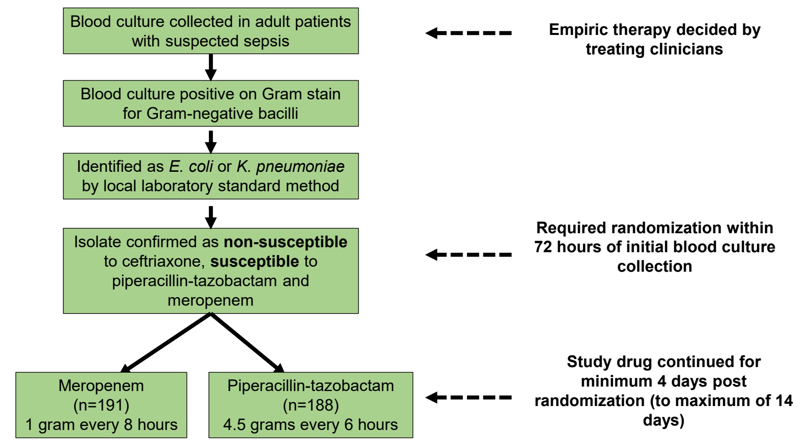
JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

Harris PNA, et al. JAMA. 2018; 320:984-994.

13



Harris PNA, et al. JAMA. 2018; 320:984-994.

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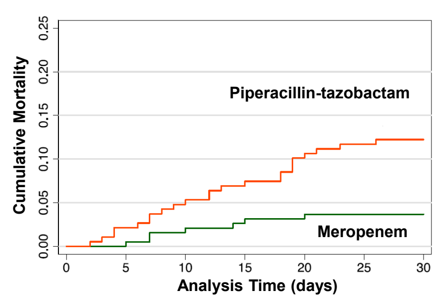
Results

- 30-day mortality
  - Piperacillin-tazobactam 12% versus meropenem 4%
  - aOR 3.41 (95% CI 1.38-8.38)
- Study terminated early as unlikely to demonstrate non-inferiority



Harris PNA, et al. JAMA. 2018; 320:984-994.

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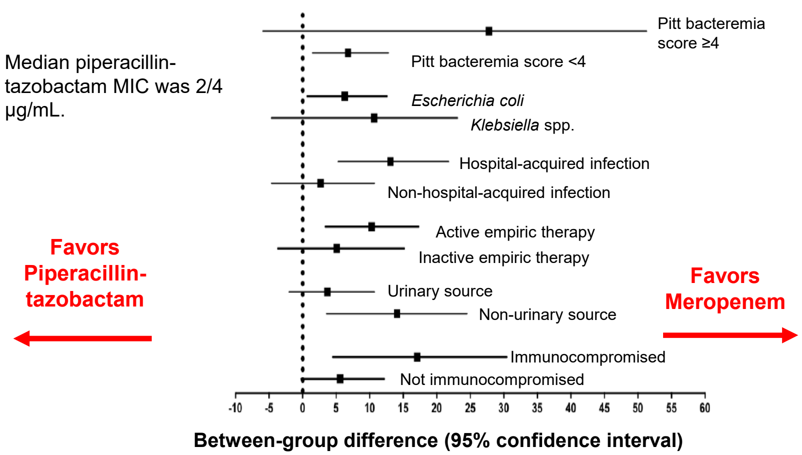
Median piperacillin-tazobactam MIC was 2/4 μg/mL.



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Speaker: Pranita Tamma, MD, MHS

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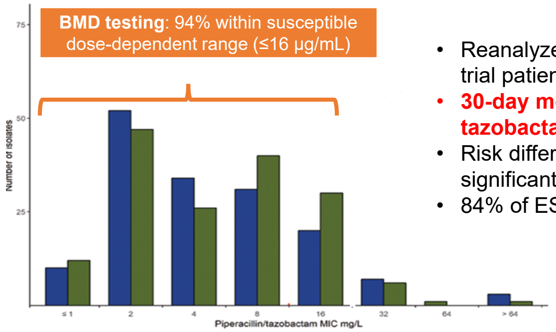
MERINO Trial: MICs for Piperacillin-Tazobactam by BMD



- Reanalyzed data from 320 of 391 trial patients
- **30-day mortality: 9% (piperacillin-tazobactam) vs. 4% (meropenem)**
- Risk difference not statistically significant (95% CI: −1% to 11%)
- 84% of ESBL genes were *bla*$_{CTX\text{-}M}$

Blue = Meropenem arm
Green = Piperacillin-tazobactam arm

Henderson A, et al. Clin Infect Dis. 2021;73:e3842-e3850.

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NIH U.S. National Library of Medicine
ClinicalTrials.gov

ClinicalTrials.gov
ID NCT03671967

PipEracillin Tazobactam Versus mERoPENem for Treatment of Bloodstream Infections Caused by Cephalosporin-Resistant Enterobacteriaceae (PETERPEN)

Study Start: May 2019
Study Completion: April 2026
Estimated Enrollment: 1,084 participants

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Selecting the Right Carbapenem

Critically Ill

- Meropenem and imipenem have shorter half-lives allowing for more frequent dosing, optimizing T>MIC
- Critically ill patients may have altered drug metabolism (e.g., augmented renal clearance), leading to suboptimal ertapenem drug levels

Hypoalbuminemia

- Ertapenem is highly protein bound (~90%), prolonging serum half-life
- With hypoalbuminemia, the free fraction of ertapenem increases, increasing ertapenem clearance
- 30-day mortality greater than 4 times higher with ertapenem compared to meropenem/imipenem for patients with hypoalbuminemia

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Cefepime for ESBL-E Infections

- CTX-M enzymes generally hydrolyze cefepime
- No clinical trials comparing cefepime and carbapenems for ESBL-E bloodstream infections
- Poorer outcomes with cefepime compared to carbapenems for the treatment of ESBL-E bloodstream infections in multiple comparative effectiveness studies

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Returning to the Clinical Case

- 18-year-old female
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Meropenem	0.5 µg/mL	S
Piperacillin-tazobactam	8/4 µg/mL	S
Tobramycin	1 µg/mL	S
Trimethoprim-sulfamethoxazole	0.5/4 µg/mL	S

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Take-Home Points: ESBL-E Bloodstream Infections

- Pre-clinical and clinical data support the use of **carbapenems** for ESBL-E bloodstream infections, at least initially
  - **Meropenem/imipenem:** Preferred over ertapenem while patient critically ill or with low albumin; otherwise ertapenem reasonable
  - **Piperacillin-tazobactam**: Not preferred for bloodstream infections; may be reasonable for UTI if not ill-appearing and no concerns for complicated UTI (e.g., renal abscess, renal stone, indwelling stents that cannot be removed)
  - **Cefepime:** Available data do not support it for ESBL-E infections
    - **Cefepime-enmetazobactam**: May become a preferred treatment for ESBL-E infections
- Oral **TMP-SMX, ciprofloxacin, levofloxacin,** are reasonable for ESBL-E bloodstream infections, usually after some clinical improvement
  - **Sulopenem**: May become a future option for step-down therapy but not enough data at the present time

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AmpC-E Infections

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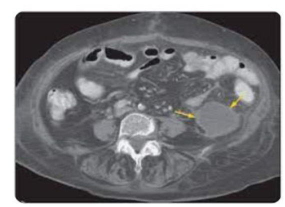
Clinical Case

- 21-year-old male with colon cancer
- Fevers, abdominal pain, and mental status changes one week after partial colectomy
- Multiple intra-abdominal abscesses
- Blood cultures growing *Enterobacter cloacae* complex



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Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	4/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	≥4/76 µg/mL	R

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Question #2

Which of the following is the preferred regimen for a patient with an intra-abdominal abscess in the setting of *Enterobacter cloacae* bacteremia, with *E. cloacae* exhibiting susceptibility to ceftriaxone, cefepime, piperacillin-tazobactam, and meropenem?

A. Cefepime plus metronidazole
B. Ceftriaxone plus metronidazole
C. Ceftazidime-avibactam
D. Meropenem-vaborbactam
E. Piperacillin-tazobactam

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Three Main Mechanisms of Excessive AmpC Production

- **Inducible chromosomal *ampC* expression**
  - Inducible *ampC* expression often in the presence of specific antibiotics
- **Stable chromosomal *ampC* de-repression**
  - Some Enterobacterales isolates (e.g., some *E. coli*) contain mutations in promoters or attenuators of *ampC* or other regulatory genes, stably de-repressing *ampC* gene expression
- **Plasmid-mediated (sometimes chromosomal) *ampC* genes**
  - *ampC* genes carried on plasmids (and integrated into chromosome of some species)
  - Examples: bla_{CMY}, bla_{FOX}, bla_{DHA}, bla_{ACT}, bla_{MIR}

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Overview of AmpC-E

- AmpC enzymes assist with bacterial cell wall recycling
  - Organisms producing AmpC enzymes even at low levels produce sufficient enzymes to hydrolyze ampicillin, ampicillin-sulbactam, cefazolin, cephamycins
- Inducible AmpC production: Capable of hydrolyzing certain antibiotics even though the bacteria initially seems susceptible to those agents
  - Most notorious = **ceftriaxone** (and other third-generation cephalosporins)
- *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes* have a reasonable likelihood of excessive AmpC production if exposed to ceftriaxone
  - Emergence of resistance while receiving ceftriaxone **~20%** of the time
- *Serratia marcescens*, *Morganella morganii*, and *Providencia* spp. are significantly less likely to have excessive AmpC production if exposed to ceftriaxone
  - Emergence of resistance while receiving ceftriaxone **<5%** of the time

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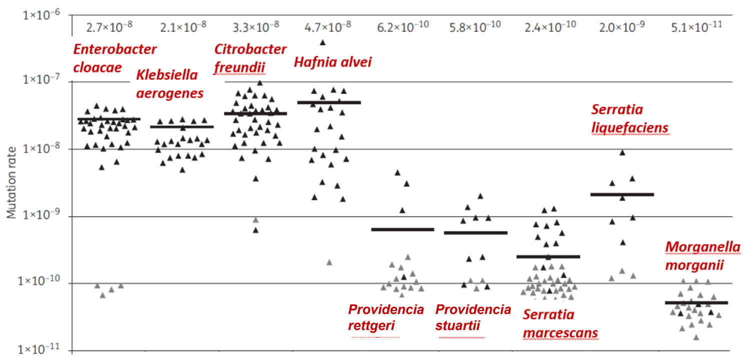

Kohlmann R, et al. J Antimicrob Chemother 2018; 73: 1530–1536.

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Changes with Antibiotic MICs with Increases AmpC Production

E. coli Isolate	bla_{CMY-2} copy number	Piperacillin-tazobactam (μg/mL)	Aztreonam (μg/mL)	Ceftazidime (μg/mL)	Cefepime (μg/mL)	Imipenem (μg/mL)	Ertapenem (μg/mL)
Parent strain	1	4	2	32	0.12	0.12	0.02
Mutant 1	13	512	64	512	4	0.5	0.38
Mutant 2	3	64	32	128	0.5	0.12	0.12
Mutant 3	7	256	32	256	1	0.25	0.19

Kurpiel KM, et al. J Antimicrob Chemother 2012; 67:339-45.

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Cefepime

- Cefepime has the advantage of both being a weak inducer of *ampC* and of withstanding hydrolysis by AmpC β-lactamases
  - It is considered a preferred agent for the treatment of AmpC-E infections

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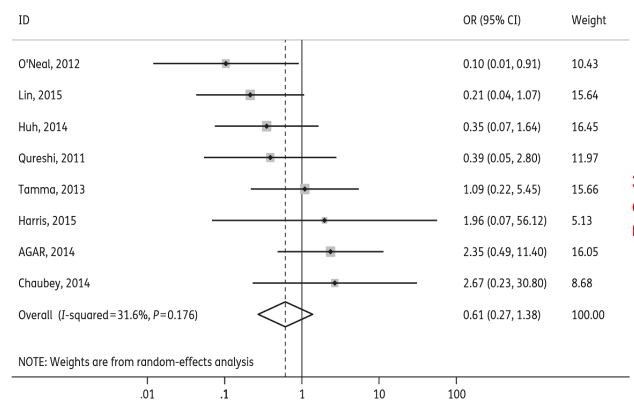

30 day mortality cefepime (9%) vs. meropenem (15%)

Favors cefepime **Favors meropenem**

Harris PNA, et al. J Antimicrob Chemother 2016; 71:296-306.

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Piperacillin-Tazobactam

- Tazobactam is less effective at inhibiting AmpC hydrolysis in vitro than newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam
- The role of piperacillin-tazobactam in treating Enterobacterales at risk for clinically significant AmpC production remains uncertain

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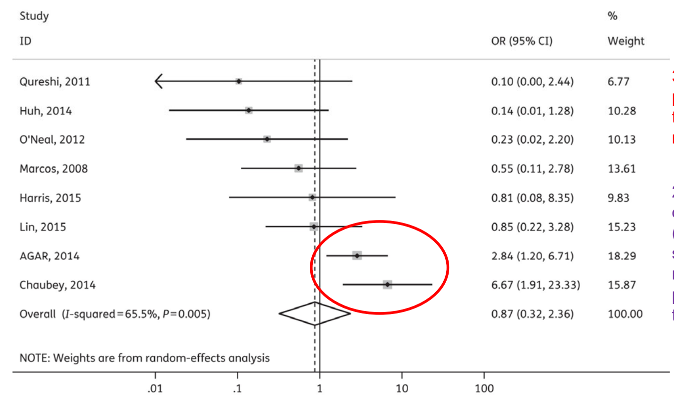

30 day mortality piperacillin-tazobactam (11%) vs. meropenem (15%)

2 additional observational studies: (n=184) with significantly higher mortality in piperacillin-tazobactam group

Harris PNA, et al. J Antimicrob Chemother 2016; 71:296-306. da Cunha, et al. Infect Drug Resist. 2021;14:3083-3097. Lu B, et al. J Antimicrob Chemother. 2023;78(4):1009-1014.

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MERINO 2

Outcomes	Piperacillin-tazobactam (n=38)	Meropenem (n=34)	P-value
Composite outcome at day 30	29%	21%	0.41
Death	0%	6%	0.13
Clinical failure	21%	12%	0.29
Microbiological failure	13%	0%	0.03
Microbiological relapse	0%	9%	0.06

Includes patients with *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp., or *Serratia marcescens* bloodstream infections

Stewart AG, et al. Open Forum Infect Dis. 2021;8:ofab387.

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Returning to the Clinical Case

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Take-Home Points: AmpC-E Infections

- Ceftriaxone is generally not suggested for the treatment of infections caused by AmpC-E, outside of uncomplicated cystitis
  - Most concerning organisms: *E. cloacae*, *K. aerogenes*, *C. freundii*
- For organisms at lower risk of moderate AmpC production (e.g., *S. marcescens*) ceftriaxone is generally sufficient
- Cefepime is generally an effective treatment option for AmpC-E infections
- Data less favorable for piperacillin-tazobactam for AmpC-E infections
- Save the carbapenems for infections where there are fewer options!
- Fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole, and doxycycline, are not substrates for AmpC hydrolysis and remain treatment options for AmpC-E infections

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CRE Infections

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Defining Carbapenem-Resistant Enterobacterales (CRE)

- Enterobacterales resistant to at least one carbapenem antibiotic
- Often produce a carbapenemase enzyme
  - *Klebsiella pneumoniae* carbapenemases (KPCs)
  - New Delhi metallo-β-lactamases (NDMs)
  - Verona integron-encoded metallo-β-lactamases (VIMs)
  - Imipenem-hydrolyzing metallo-β-lactamases (IMPs)
  - Oxacillinases (OXA-48-like)

Metallo-β-lactamases (MBLs) [NDMs, VIMs, IMPs]

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KPC-Producing Enterobacterales

- Most common carbapenemases in the United States
- Can occur with any Enterobacterales; not unique to *K. pneumoniae*

- **Treatment options**
  - Preferred: Meropenem-vaborbactam > ceftazidime-avibactam > imipenem-cilastatin-relebactam
  - Alternative: Cefiderocol

Sabour S, et al. Antimicrob Agents Chemother 2021; 65(e0110521). van Duin D, et al. Lancet Infect Dis 2020; 20:731-741.

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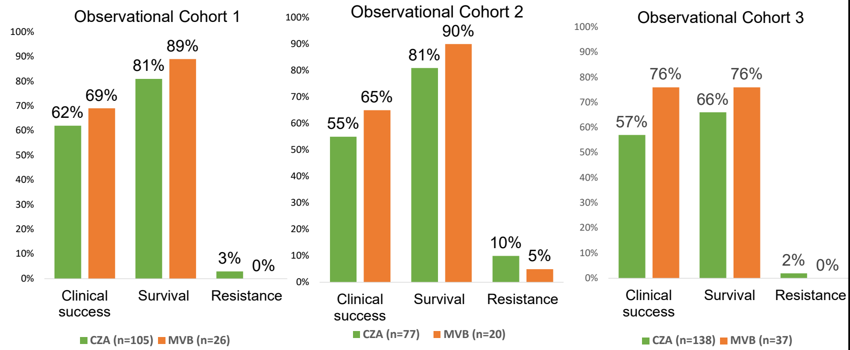
Ceftazidime-Avibactam Versus Meropenem-Vaborbactam



Ackley R, et al. AAC 2020; e02313-19. Tumbarello M, et al. JAR AMR 2022;4(1):dlac022. Tumbarello M, et al. Clin Infect Dis. 2019; 68(3):355-364. Shields RK, et al. Antimicrob Ag Chemother. 2018; 62(5):e02487-17. Shields RK, et al. Clin Infect Dis. 2020;71(3):667-671.

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NDM-Producing Enterobacterales

- Rare but increasing in the United States
- Main risk factor: previous medical care in Indian subcontinent; but clear risk factors not always present

- **Treatment options**
  - Preferred: aztreonam-avibactam (or if not available, ceftazidime-avibactam PLUS aztreonam); cefiderocol
  - Comparative effectiveness studies between the two agents not available

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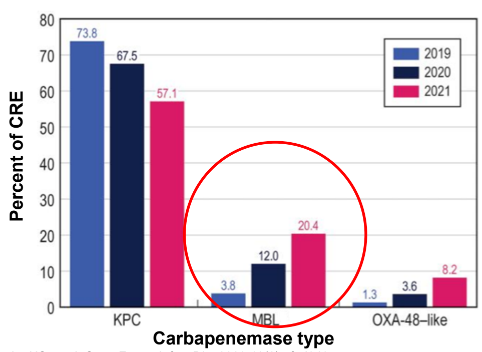
NDM-Enterobacterales are Rapidly Rising in the United States



- Data from 74 United States medical centers
- NDM represent 88% for metallo-beta-lactamases

Sader HS, et al. Open Forum Infect Dis. 2023;10(2):ofad046.

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A Brief Overview of NDM-Producing Enterobacterales

- Require zinc at their active site for β-lactam hydrolysis
  - Variants with lower zinc requirements emerging, enabling them to thrive in settings of relative zinc scarcity, which is common in states of human infection
- Easy transferability of bla_{NDM} between species on mobile genomic elements
- bla_{NDM} detected in 2008 in *K. pneumoniae* and *E. coli* isolates from a patient returning to Sweden from India
  - By 2010, NDM-producing bacteria in drinking water in New Delhi
- Over 60 different variants of NDM circulating

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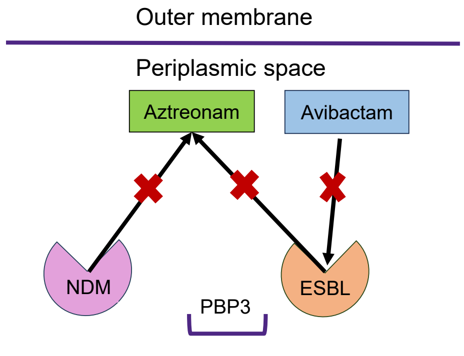
Aztreonam-Avibactam: Mechanism of Action



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Aztreonam-Avibactam: Activity Against MBL-Producing Enterobacterales

Enzyme	n	MIC ≤4 µg/mL	MIC 90 µg/mL
NDM	1421	98%	0.5
VIM	242	100%	1
IMP	49	100%	1
All MBL	1707	98%	1

Rosolini GM, et al. J Glob Antimicrob Resist. 2024:123-131.

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Cefiderocol

- Innate immune system minimizes free iron in response to bacterial infections
  - Most iron bound to hemoglobin, myoglobin, or iron binding proteins
- Bacteria upregulate production of their native siderophores
  - Iron-chelating compounds that scavenge for free iron
- Cefiderocol is a siderophore (competing with bacterial siderophores) conjugated to a cephalosporin
- "Trojan Horse" approach to enter bacteria through iron transport channels
  - Not impacted by porins or efflux pumps
  - Once across outer membrane, cefiderocol dissociates from iron molecule and binds to PBP3, disrupting cell wall synthesis

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Emergence of Resistance to Aztreonam-Avibactam & Cefiderocol

- Aztreonam and cefiderocol bind primarily to PBP3
- 4 amino acid PBP3 insertions result in inactivity of aztreonam-avibactam and cefiderocol MICs, particularly when present with CMY (i.e., AmpC) enzymes
- Represent >50% of NDM-producing *E. coli* in India
  - Now present in all regions of the world

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301 DVFEPGSTVKPMVVMTALQRGVVRENSVLNTIPYRIKYRINGHEIKDVARYSELTLTGVL 360
    DVFEPGSTVKPMVVMTALQRGVVRENSVLNTIPYRIKYRINGHEIKDVARYSELTLTGVL
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CRE: Take-Home Points

- KPC: most common carbapenemase globally
- NDM: hint medical care in South Asia

- **Preferred treatment**
  - KPC-producers: meropenem-vaborbactam > ceftazidime-avibactam > imipenem-cilastatin-relebactam
  - NDM-producers: cefiderocol = aztreonam-avibactam (if not available, ceftazidime-avibactam PLUS aztreonam)

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