



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

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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)

Clinical Infectious Diseases
IDSA GUIDELINES



Infectious Diseases Society of America 2026 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,^{1,*} Robert A. Bonomo,² Emily L. Heil,³ Julie Ann Justo,⁴ Michael J. Sattin,⁵ and Amy J. Mathers⁶

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/

ESBL-E Infections

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*



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 2026 breakpoints

Antibiotic	MIC	Interpretation*
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*Applying Clinical and Laboratory Standards Institute 2026 breakpoints

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

Question #1

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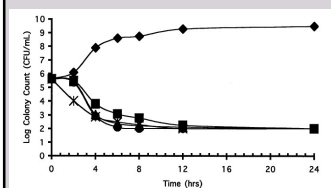
- A. Ceftriaxone
- B. Piperacillin-tazobactam
- C. Cefepime
- D. Meropenem***
- E. Ceftazidime-avibactam

A Primer on ESBL-E

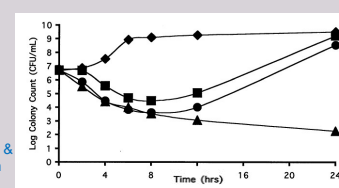
- ESBLs are enzymes that inactivate penicillins, cephalosporins, and aztreonam
 - Do not inactivate non- β -lactam agents (e.g., aminoglycosides, TMP-SMX, ciprofloxacin, doxycycline)
 - Organisms carrying ESBL genes often harbor antimicrobial resistance determinants to a broad range of antibiotics
- 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 $\mu\text{g/mL}$** 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

Piperacillin-Tazobactam (PTZ): Inoculum Effect

Caveat: Relevance to clinical practice?



Low inoculum ESBL growth curve



High inoculum ESBL growth curve

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

What are Some Concerns with Tazobactam as an ESBL Inhibitor?

- Designed to inhibit SHV and TEM ESBL variants and not CTX-M ESBLs
- 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
- Piperacillin-tazobactam breakpoint for Enterobacterales exclusively based on pharmacokinetic-pharmacodynamic considerations of piperacillin and not tazobactam

JAMA

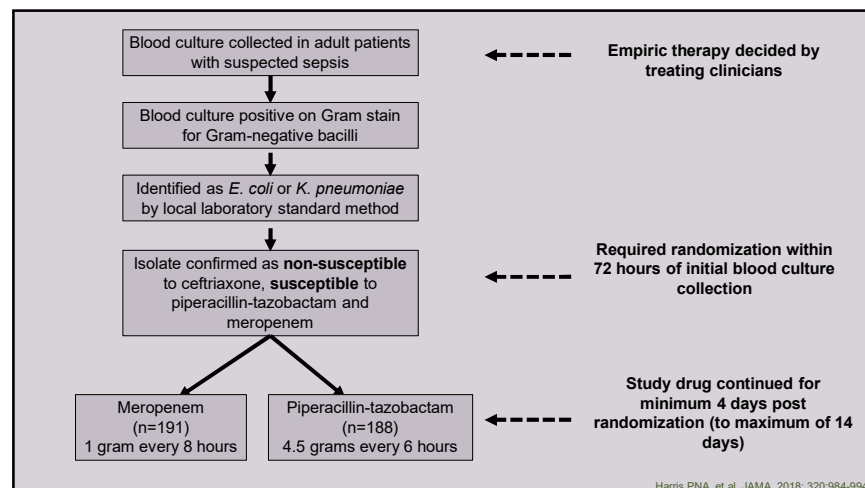
Research

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 Bhalily, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Myakis, 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 Lorenz, 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)

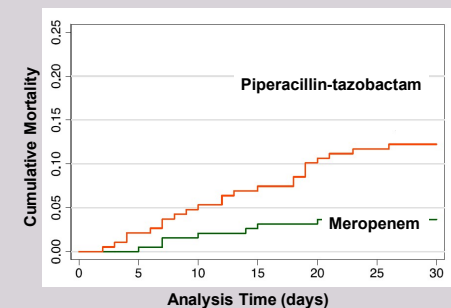
Harris PNA, et al. JAMA. 2018; 320:984-994.



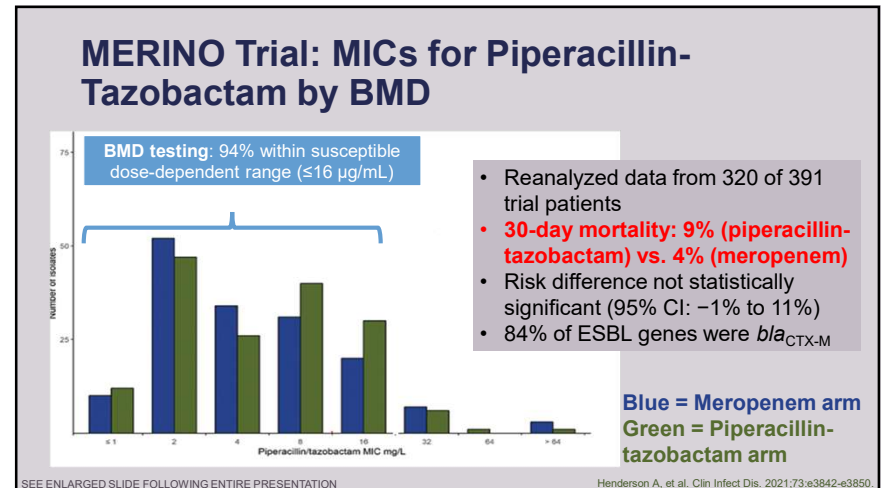
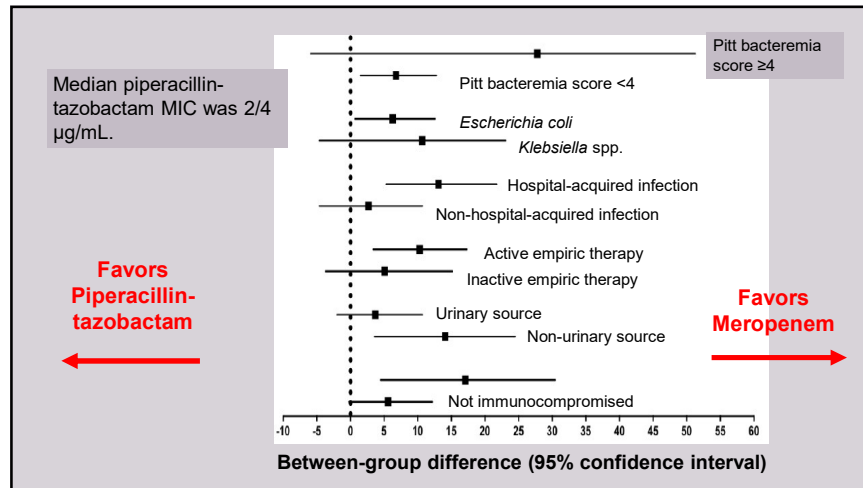
Harris PNA, et al. JAMA. 2018; 320:984-994.

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.



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

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

Returning to the Clinical Case

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Trimethoprim-sulfamethoxazole	0.5/4 µg/mL	S

Take-Home Points ESBL-E Bloodstream Infections

- Bloodstream infections
 - Preferred: **Meropenem/imipenem** (preferred over ertapenem while patient critically ill or with low albumin; otherwise ertapenem reasonable)
 - Alternate: Cefepime-enmetazobactam
 - Oral transition options: TMP-SMX, ciprofloxacin, levofloxacin
- Complicated UTIs
 - Preferred: **TMP-SMX, ciprofloxacin, or levofloxacin, cefepime-enmetazobactam, or carbapenems** (ertapenem, meropenem, imipenem, oral tebipenem)
 - Alternates: IV fosfomycin, aminoglycosides, and piperacillin-tazobactam
 - Oral transition options: Sulopenem

AmpC-E Infections

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



Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	S
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	16 µg/mL	R
Cefepime	≤1 µg/mL	S
Ceftriaxone	1 µg/mL	S
Ciprofloxacin	0.25 µg/mL	S
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
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

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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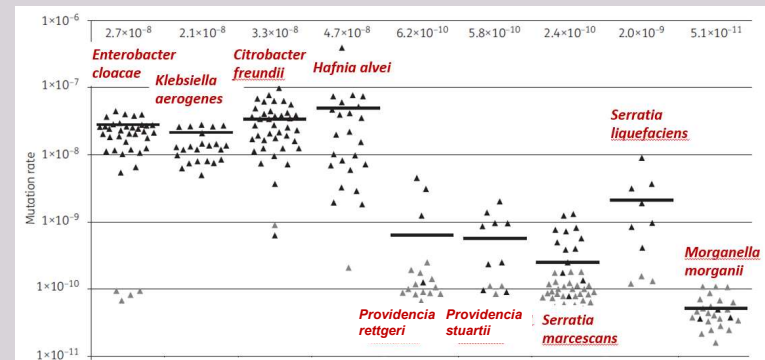
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Three Main Mechanisms of Excessive AmpC Production

- **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 (e.g., *ampD*), stably de-repressing *ampC* gene expression
- **Plasmid-mediated (sometimes chromosomal) *ampC* gene expression**
 - *ampC* genes carried on plasmids (and integrated into chromosome of some species)
 - Examples: *bla*_{CMY}, *bla*_{FOX}, *bla*_{DHA}, *bla*_{ACT}, *bla*_{MIR}

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* (and likely *Hafnia alvei*) 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



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

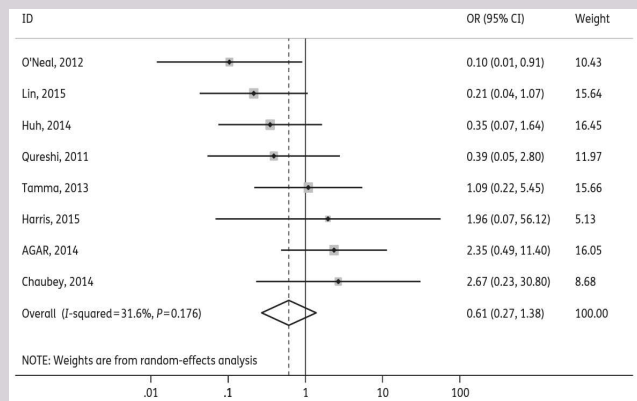
Changes with Antibiotic MICs with Increases AmpC Production

<i>E. coli</i> 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

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



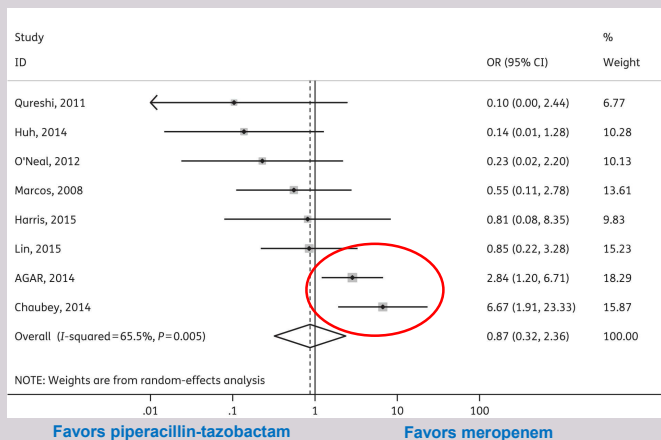
30 day mortality
cefepime (9%) vs.
meropenem (15%)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

Piperacillin-Tazobactam

- Tazobactam is significantly 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, but is not suggested according to the IDSA AMR Treatment Guidance



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

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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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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*, *H. alvei*
- 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

CRE Infections

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 (IMP)
 - Oxacillinases (OXA-48-like)

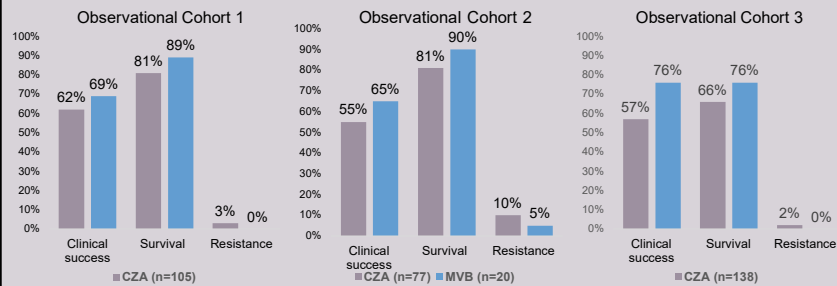
} Metallo- β -lactamases (MBLs)

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.

Ceftazidime-Avibactam Versus Meropenem-Vaborbactam

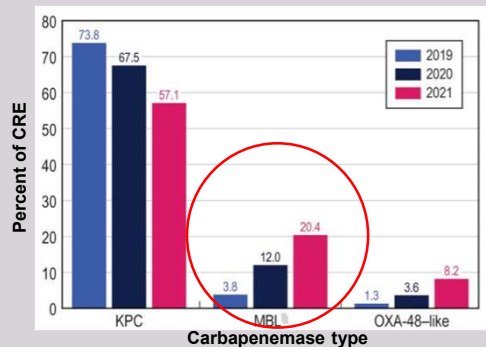


Karaba SM, Antimicrob Agents Chemother. 2026 May 6;70(5):e0160225. Ackley R, et al. AAC 2020; e02313-19. Tumbarello M, et al. JAR AMR 2022;4(1):dlac022. Tumbarello M, et al. Clin Infect Dis. 2019; 68(3):355-364. Shields RK, et al. Antimicrob Ag Chemother. 2018; 62(5):e02487-17. Shields RK, et al. Clin Infect Dis. 2020;71(3):667-671.

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

NDM-Enterobacterales are Rapidly Rising in the United States



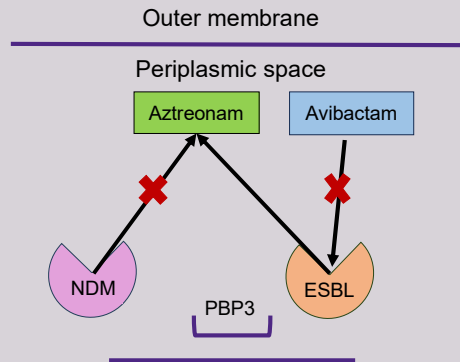
- Data from 74 United States medical centers
- NDM represent 88% of metallo-beta-lactamases
 - Most commonly *K. pneumoniae*

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

A Brief Overview of NDM-Producing Enterobacterales

- *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
- 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 bacterial species via mobile genomic elements

Aztreonam-Avibactam Mechanism of Action



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

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 ~90% of NDM-producing *E. coli* in India
 - Now present in all regions of the world

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DVFEPGSTVKPMVMTALQGVVRENSVLNTIF YRI YRINGHEIKDVARYSELTLTGVL
DVFEPGSTVKPMVMTALQGVVRENSVLNTIF YRI YRINGHEIKDVARYSELTLTGVL
DVFEPGSTVKPMVMTALQGVVRENSVLNTIF YRI YRINGHEIKDVARYSELTLTGVL
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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)
 - May 2026: cefepime-zidebactam FDA-approved