13th ACCP 2023
Meeting on Antimicrobial Chemotherapy in Clinical Practice (ACCP)
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Aztreonam/avibactam, plazomicina e eravaciclina

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Aztreonam/avibactam

- Aztreonam is not hydrolyzed by MBLs, but is generally cleaved by other clinically relevant serine-β-lactamase

- Avibactam, a non- β -lactam β -lactamase inhibitor, may restore the efficacy of a β -lactam against CRE-producing Ambler class A (KPC) and Ambler class D (OXA-48 and 48-like) serine carbapenemases.

In vitro activity of aztreonam-avibactam against Enterobacterales isolates collected in Latin America, Africa/Middle East, Asia, and Eurasia for the ATLAS Global Surveillance Program in 2019-2021

Wise M Eur J Clin Microbiol Infect Dis 2023 Sep;42(9):1135-1143.

	ATM–AVI		ATM		AMK		FEP		CAZ		CZA		CST[c]		IPM		LVX		MEM		TGC[d]	
	MIC_{90}	**% ≤ 8 (mg/L[e])**	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
All (24,937)	**0.25**	**99.8**	> 64	59.9	16	91.3	> 32	60.6	> 64	59.6	1	93.1	> 8	81.5	8	77.0	> 8	54.8	16	86.9	2	96.4
MDR (12,192)	**0.5**	**99.5**	> 64	18.3	> 64	82.3	> 32	20.0	> 64	18.6	> 64	86.0	> 8	82.7	> 8	62.1	> 8	20.8	> 16	73.3	2	93.4
XDR (2974)	**1**	**98.7**	> 64	5.8	> 64	42.1	> 32	1.2	> 64	2.2	> 64	47.6	> 8	77.2	> 8	6.0	> 8	2.7	> 16	12.1	4	88.6
CRE (3289)	**1**	**99.1**	> 64	12.4	> 64	50.0	> 32	4.7	> 64	6.6	> 64	49.9	> 8	79.6	> 8	0.8	> 8	10.7	> 16	5.4	2	94.4
MBL (1610)	**2**	**98.8**	> 64	16.1	> 64	42.2	> 32	0.4	> 64	0.2	> 64	1.0	> 8	83.4	> 8	0.9	> 8	9.6	> 16	1.8	2	93.8
KPC+ (705)	**0.5**	**100**	> 64	0.7	64	69.6	> 32	4.4	> 64	10.1	2	99.0	> 8	71.1	> 8	1.6	> 8	13.6	> 16	4.0	2	95.0
OXA-48-like+ (831)	**0.5**	**99.6**	> 64	8.2	> 64	46.7	> 32	5.2	> 64	7.9	2	98.0	> 8	81.7	> 8	8.2	> 8	3.9	> 16	13.8	2	95.8
ESBL+ (3605)	**0.25**	**99.6**	> 64	5.7	16	92.7	> 32	4.8	> 64	13.0	1	98.9	1	96.3	> 8	21.8	> 8	21.8	0.12	95.0	1	97.2

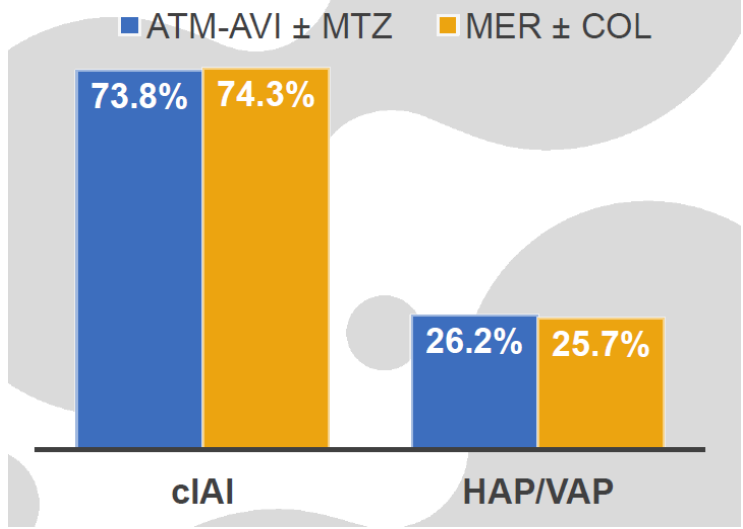
Efficacy and Safety of Aztreonam-Avibactam for the Treatment of Serious Infections Due to Gram-Negative Bacteria, Including Metallo-β-Lactamase-Producing Pathogens: Phase 3 REVISIT Study

- phase 3, prospective, randomized, multicenter, open-label, central assessor-blinded study in hospitalized adults.
- Patients were randomized 2:1 to
  1. ATM-AVI (± metronidazole [MTZ]; cIAI patients only) or
  2. meropenem (MER) ± colistin (COL)
     - for 5–14 (cIAI) or 7–14 (HAP/VAP) days.
- Clinical cure at the test-of-cure (TOC) visit in the intent-to-treat (ITT) and clinically evaluable (CE) analysis sets were the primary efficacy endpoints. Key secondary endpoints included microbiological responses at TOC, 28-day mortality, and safety. No formal hypothesis testing was planned.

Efficacy and Safety of Aztreonam-Avibactam for the Treatment of Serious Infections Due to Gram-Negative Bacteria, Including Metallo-β-Lactamase-Producing Pathogens: Phase 3 REVISIT Study

	cIAI		HAP/VAP		Overall	
	ATM-AVI + MTZ (n=208)	MER ± COL (n=104)	ATM-AVI (n=74)	MER ± COL (n=36)	ATM-AVI ± MTZ (n=282)	MER ± COL (n=140)
Age (years), mean (SD)	52.4 (17.7)	50.5 (15.8)	63.0 (16.0)	64.3 (13.4)	55.2 (17.8)	54.0 (16.3)
Male, n (%)	133 (63.9)	71 (68.3)	53 (71.6)	30 (83.3)	186 (66.0)	101 (72.1)
CLCR, mL/min, median (range)	102.0 (20.1, 337.0)	94.0 (29.0, 305.0)	88.0 (19.0, 317.0)	88 (38.0, 404.0)	100.0 (19.0, 337.0)	92.0 (29.0, 404.0)
APACHE II score, mean (SD)	7.5 (5.2)	7.7 (5.1)	16.4 (5.1)	17.3 (5.6)	9.8 (6.5)	10.1 (6.7)
Previous treatment failure, n (%)	25 **(12.0)**	10 **(9.6)**	50 **(67.6)**	20 **(55.6)**	75 **(26.6)**	30 **(21.4)**

- Majority of patients had a diagnosis of cIAI



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Carmeli Y et al IDWeek 2023, Boston, MA, USA October 11–15, 2023

Efficacy and Safety of Aztreonam-Avibactam for the Treatment of Serious Infections Due to Gram-Negative Bacteria, Including Metallo-β-Lactamase-Producing Pathogens: Phase 3 REVISIT Study

	cIAI		HAP/VAP		Overall	
	ATM-AVI + MTZ (n=208)	MER ± COL (n=104)	ATM-AVI (n=74)	MER ± COL (n=36)	ATM-AVI ± MTZ (n=282)	MER ± COL (n=140)
Cure, n (%) [95%CI]	159 **(76.4)** [70.3, 81.8]	77 **(74.0)** [65.0, 81.7]	34 **(45.9)** [34.9, 57.3]	15 **(41.7)** [26.7, 57.9]	193 **(68.4)** [62.8, 73.7]	92 **(65.7)** [57.6, 73.2]
Difference† (95% CI‡)	2.4 (-12.4, 19.1)		4.3 (-25.6, 32.2)		2.7 [-11.4, 17.8]	
Failure, n (%)	34 (16.3)	23 (22.1)	33 (44.6)	17 (47.2)	67 (23.8%)	40 (28.6%)
Indeterminate, n (%)	15 (7.2)	4 (3.8)	7 (9.5)	4 (11.1)	22 (7.8%)	8 (5.7%)

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	cIAI		HAP/VAP		Overall	
% (n/N)	ATM-AVI + MTZ (N=208)	MER ± COL (N=104)	ATM-AVI (N=74)	MER ± COL (N=36)	ATM-AVI ± MTZ (N=282)	MER ± COL (N=140)
28-day all-cause mortality	**1.9** (4/208)	**2.9** (3/104)	**10.8** (8/74)	**19.4** (7/36)	**4.3** (12/282)	**7.1** (10/140)
Mortality cause						
Disease under study	0	0	4.1 (3/74)	2.8 (1/36)	1.1 (3/282)	0.7 (1/140)
Other	1.9 (4/208)	1.9 (2/104)	6.8 (5/74)	16.7 (6/36)	3.2 (9/282)	5.7 (8/140)
Unknown	0	1.0 (1/104)	0	0	0	0.7 (1/140)

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MBL-positive status

Micro-ITT analysis set		
	ATM-AVI ± MTZ	MER ± COL
N	7	3
Cure n (%)	2 **(28.6)**	2 **(66.7)**
Failure n (%)	3 (42.9)	1 (33.3)
Indeterminate n (%)	2 (28.6)	0

ME analysis set		
	ATM-AVI ± MTZ	MER ± COL
N	4	1
Cure n (%)	**2 (50.0)**	**0 (0)**
Failure n (%)	2 (50.0)	1 (100)

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Plazomicin

- Prenteral aminoglycoside recently approved by the FDA for the treatment of cUTI,
- Stable against the inactivation by aminoglycoside-modifying enzymes
- 16S rRNA methyltransferases conferring resistance to virtually all aminoglycoside
- Plazomicin (89.2% to 95.9% susceptible) displayed greater activity than amikacin (72.5% to 78.6%), gentamicin (30.4% to 45.9%), and tobramycin (7.8% to 22.4%) against carbapenem-resistant and extensively drug-resistant isolate

Castanheria M Antimicrob Agents Chemother 2020 Apr 21;64(5):e02418-19.

Once-Daily Plazomicin for Complicated Urinary Tract Infections

Wagenlehner FME et al. N Engl J Med 2019; 380:729-740

- Multicenter, multinational, randomized, double-blind, phase 3 trial
- Creatinine clearance > 30 ml per minute
- Plazomicin (15 mg/Kg once daily) or meropenem (1 g every 8 hours), option for oral step-down therapy after a minimum of 4 days of IV, for a total of 7 to 10 days of therapy
- Composite cure (clinical cure and microbiologic eradication) at day 5 and at the test-of-cure visit (15 to 19 days after initiation of IV therapy with the assigned trial drug)
- 15% non inferiority margin

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Once-Daily Plazomicin for Complicated Urinary Tract Infections

Wagenlehner FME et al. N Engl J Med 2019; 380:729-740

	Plazomicin N=191 (%)	Meropenem N=197 (%)	Difference (95%CI)
Age yr	58.8±18	60±18	
Male sex	84 (44)	99 (50.3)	
cUTI	107 (56)	119 (60.4)	
Acute pyelonephritis	84 (44)	78 (40)	
Bacteremia	25 (13)	23 (12)	
ESBL phenotype	50/189 (26.5)	57/193 (29.5)	
Composite cure at day 5	168 (88)	180 (91.4)	-3.4 (-10.0 to 3.1)
Composite cure at TOC	156 (81.7)	138 (70.1)	11.6 (2.7 to 20.3)
ESBL-E	**42/51 (82.4)**	**45/60 (75)**	**7.4 (-9.6 to 23.1)**

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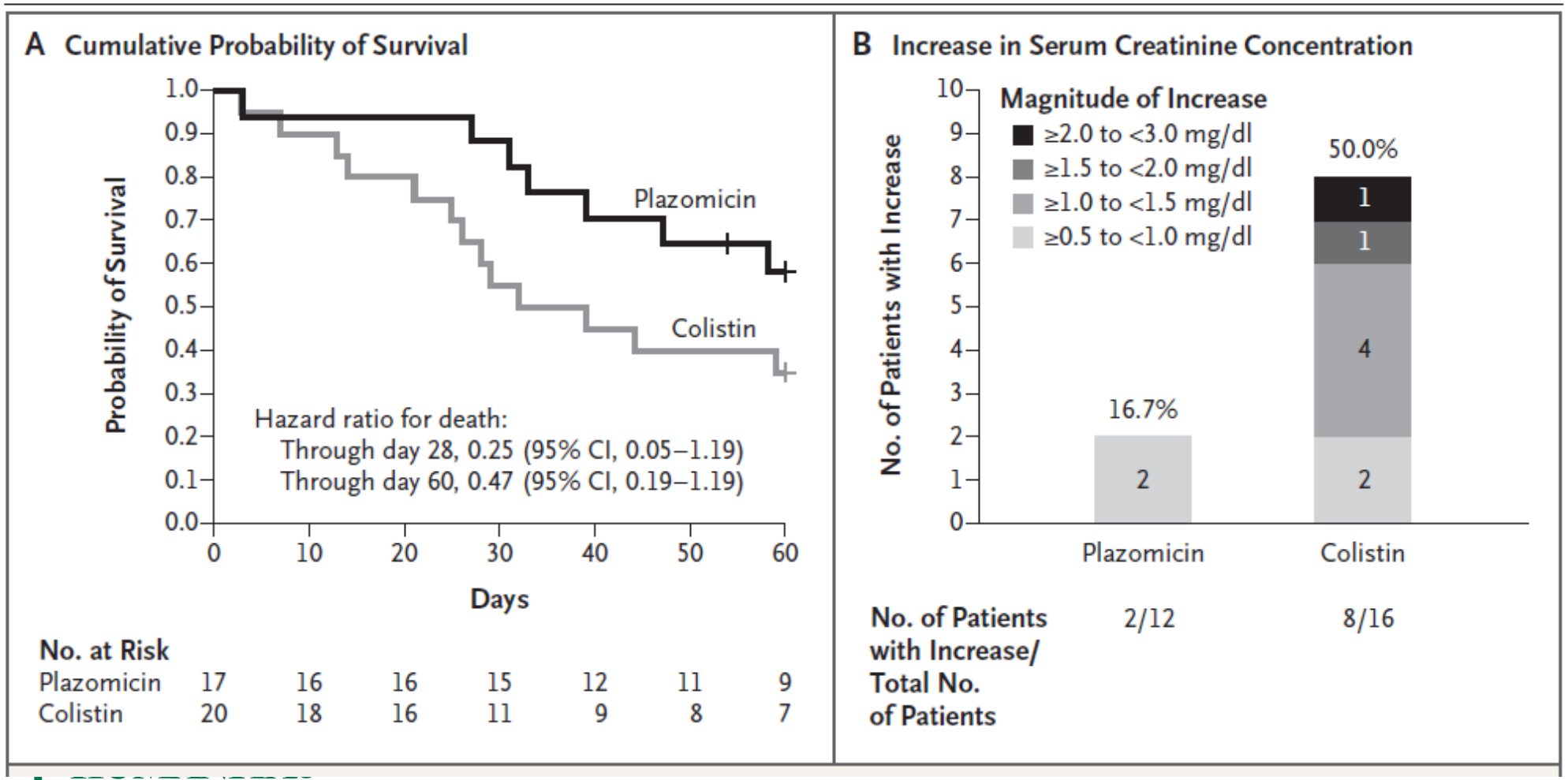
Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae



N Engl J Med 2019 Feb 21;380(8):791-793.

Eravacyclin

- Semisyntetic fluorocycline tetracycline
- Modifications at the C-7 and C-9 positions on the tetracycline core
- bind reversibly to the 30S ribosomal subunit with high affinity

Organism	Eravacycline	Tigecycline	Ertapenem	Levofloxacin	Meropenem
Gram positive					
Staphylococcus aureus	0.015–0.12	0.03–0.25	0.06–0.25	0.06–0.5	0.03–0.12
Enterococcus faecalis	0.015–0.06	0.03–0.12	4–16	0.25–2	2–8
Streptococcus pneumonia	0.004–0.03	0.015–0.12	0.03–0.25	0.5–2	0.03–0.25
Gram negative					
Escherichia coli	0.03–0.12	0.03–0.25	0.004–0.015	0.008–0.06	0.008–0.06
Pseudomonas aeruginosa	2–16	–	2–8	0.5–4	0.25–1
Haemophilus influenza	0.06–0.5	0.06–0.5	0.015–0.06	0.008–0.03	0.03–0.12
Anaerobes					
Bacteroides fragilis	0.06–0.25	0.12–1	0.06–0.25	–	0.03–0.25
Bacteroides thetaiotaomicron	0.12–1	0.5–2	0.25–1	–	0.125–0.5
Clostridium difficile	0.06–0.25	0.125–1	–	–	0.5–4

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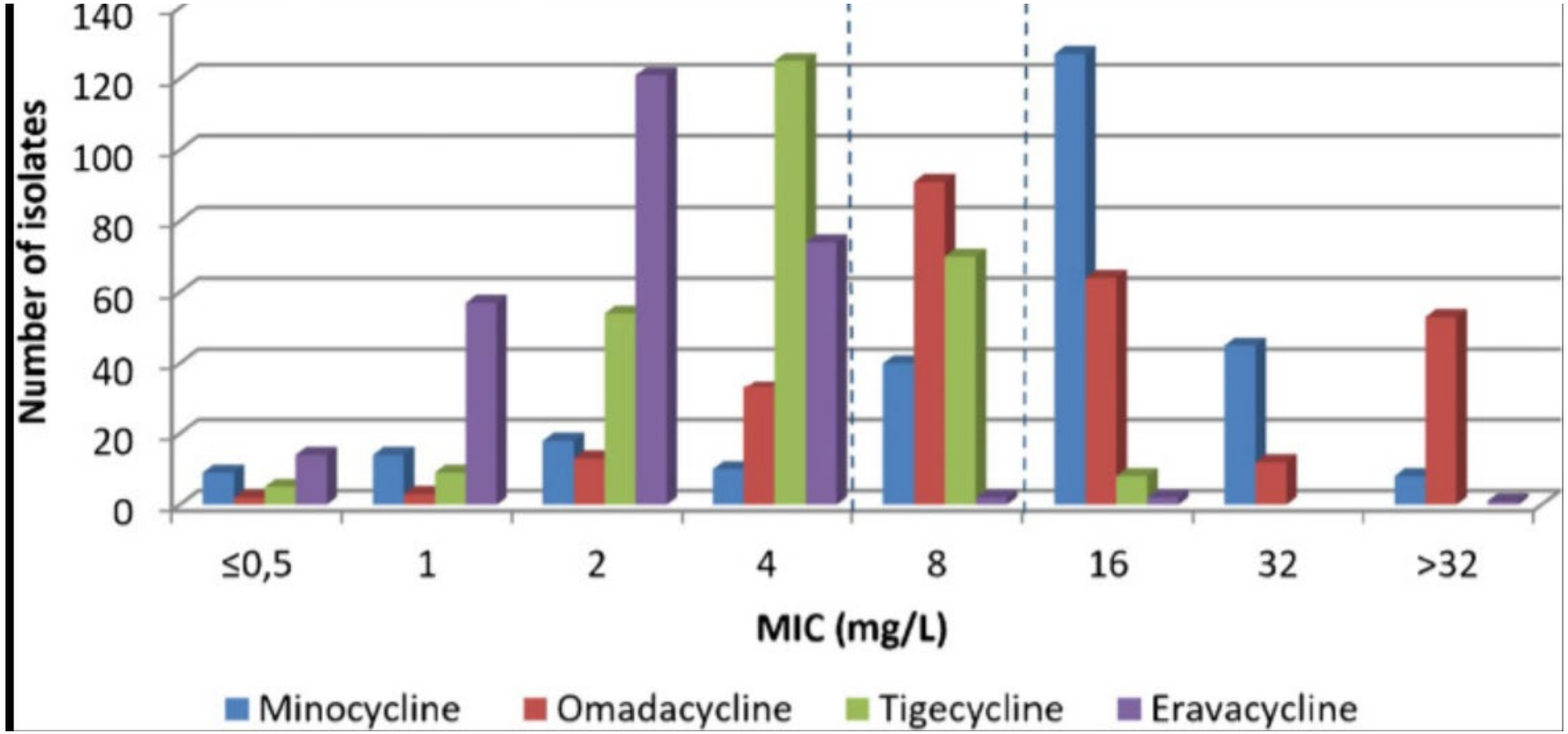
Haney M et al. Annals of Pharmacotherapy 2019, Vol. 53(11) 1124– 1135

In vitro activities of omadacycline, eravacycline, cefiderocol, apramycin, and comparator antibiotics against Acinetobacter baumannii causing bloodstream infections in Greece, 2020-2021: a multicenter study

Galani I et al Eur J Clin Microbiol Infect Dis. 2023; 42(7): 843–852.



Eravacyclin MIC50/90 = 2/4

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Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial A Randomized Clinical Trial

Solomkin J et al JAMA Surg. 2017;152(3):224-232.

- phase III, randomized, double-blind, multicenter study
- cIAI with cIAI requiring surgical or percutaneous intervention

- Ertapenem 1g in patients.
- Eravacycline 1mg/kg/12h

Table 2. Primary Efficacy Analysis for US Food and Drug Administration (Clinical Response at TOC Visit)

Population	No. (%) Eravacycline, 1.0 mg/kg Every 12 h	No. (%) Ertapenem, 1.0 g Every 24 h	Difference (95% CI)
MITT			
No.	270	268	−1.80 (−7.4 to 3.8)
Clinical cure	235 (87.0)	238 (88.8)	
Clinical failure	19 (7.0)	15 (5.6)	
Indeterminate/missing	16 (5.9)	15 (5.6)	
Micro-ITT			
No.	220	226	−0.80 (−7.1 to 5.5)
Clinical cure	191 (86.8)	198 (87.6)	
Clinical failure	19 (8.6)	11 (4.9)	
Indeterminate/missing	10 (4.5)	17 (7.5)	
CE			
No.	239	238	−1.7 (−6.3 to 2.8)
Clinical cure	222 (92.9)	225 (94.5)	
Clinical failure	17 (7.1)	13 (5.5)	
Microbiologically evaluable			
No.	198	199	−3.6 (−8.9 to 1.5)
Clinical cure	181 (91.4)	189 (95.0)	
Clinical failure	17 (8.6)	10 (5.0)	

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IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections

Solomkin J et al. Clin Infect Dis 2019 Aug 30;69(6):921-929.

Population	Eravacycline	Meropenem	Difference (95% Confidence Interval)
Modified intent-to-treat	N = 250	N = 249	…
Clinical cure	231 (92.4)	228 (91.6)	0.8 (–4.1, 5.8)
Clinical failure	7 (2.8)	9 (3.6)	…
Indeterminate/Missing	12 (4.8)	12 (4.8)	…
Microbiological intent-to-treat	N = 195	N = 205	…
Clinical cure	177 (90.8)	187 (91.2)	–0.5 (–6.3, 5.3)
Clinical failure	7 (3.6)	7 (3.4)	…
Indeterminate/Missing	11 (5.6)	11 (5.4)	…
Clinically evaluable	N = 225	N = 231	…
Clinical cure	218 (96.9)	222 (96.1)	0.8 (–2.9, 4.5)
Clinical failure	7 (3.1)	9 (3.9)	…
Indeterminate/Missing	0	0	…
Microbiologically evaluable	N = 174	N = 194	…
Clinical cure	167 (96.0)	187 (96.4)	–0.4 (–4.9, 3.8)
Clinical failure	7 (4.0)	7 (3.6)	…
Indeterminate/Missing	0	0	…

IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections

Solomkin J et al. Clin Infect Dis 2019 Aug 30;69(6):921-929.

	Eravacycline (Cured/Total)	Meropenem (Cured/Total)
Citrobacter freundii	0	1/1
CTX-M-15	0	1/1
Enterobacter cloacae/ asburiae	3/3	1/1
CTX-M-15	2/2	1/1
Escherichia coli	8/10	5/7
CTX-M-15	7/8	3/5
CTX-M-3	0/1	1/1
CTX-M-32	1/1	0
CTX-M-5	0	1/1
SHV-12	0	1/1
Klebsiella pneumoniae	5/5	5/6
CTX-M-15	5/5	3/4
CTX-M-2	0	1/1
SHV-12	0	1/1
Serratia marcescens	0	1/1
CTX-M-15	0	1/1

Table 9. Incidence of Adverse Events Occurring in >2% of Patients in Either Group: Safety Population

Medical Dictionary for Regulatory Activities Term	Eravacycline (N = 250)	Meropenem (N = 249)
Nausea	12 (4.8)	2 (0.8)
Vomiting	9 (3.6)	5 (2.0)
Infusion site phlebitis	8 (3.2)	1 (0.4)
Infusion site thrombosis	6 (2.4)	1 (0.4)
Wound infection (superficial)	7 (2.8)	4 (1.6)
Diarrhea	6 (2.4)	3 (1.2)
Anemia	3 (1.2)	6 (2.4)
Hypertension	2 (0.8)	7 (2.8)
Hypokalemia	0	6 (2.4)
Discontinued because of adverse event	4 (1.6)	4 (2.0)

A retrospective, multicentre evaluation of eravacycline utilisation in community and academic hospitals

Hobbs A et al J Glob Antimicrob Resist 2022 Jun:29:430-433. doi: 10.1016/j.jgar.2021.10.020

- 66 patients
- Infections sites included pulmonary (34.8%), intra-abdominal (31.8%), skin/soft tissue (28.8%), bone/joint (13.6%) and line-associated bacteraemia (4.5%)
- BSI 18%
- Monotherpy 62%
- Microbiology available 40/66:
  - Acinetobacter (30%), CRE (7%) and VRE (30%)
- Clinical improvement: 95% (100 in BSI)
- Full resolution: 86% (91.7 in BSI

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Efficacy of Eravacycline Versus Best Previously Available Therapy for Adults With Pneumonia Due to Difficult-to-Treat Resistant (DTR) Acinetobacter baumannii

Scott C et al. Ann Pharmacother 2022 Dec;56(12):1299-1307.

- 93 patients
- 27 received eravacycline
- Eravacycline was associated with
  - higher 30-day mortality (33% vs 15%; P = 0.048),
  - lower microbiologic cure (17% vs 59%; P = 0.004),
  - longer durations of mechanical ventilation (10.5 vs 6.5 days; P = 0.016).
  - At baseline, eravacycline patients had more A. baumannii bacteremia and coinfection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

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	Enterobacterales			
	ESBL	**AmpC**	**OXA 48**	**MBL**
Aztreonam avibactam	✓	✓	✓	✓
Plazomicin	✓	✓	-/+	-/+
Eravacycline	✓	✓	✓	✓

	Acinetobacter baumannii		
	AmpC	**OXA-23; OXA-40; OXA-50**	**IMP/VIM/NDM**
Aztreonam avibactam	X	X	X
Plazomicin	X	X	X
Eravacycline	✓	✓	✓

	Pseudomonas aeruginosa			
	AmpC	**Efflux pomp**	**Loss of Porine**	**MBL**
Aztreonam avibactam	--/+	--	--	--/+
Plazomicin	✓	+/-	-/+	-/+
Eravacycline	X	X	X	X

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