YENİ ANTİMİKROBİYALLER

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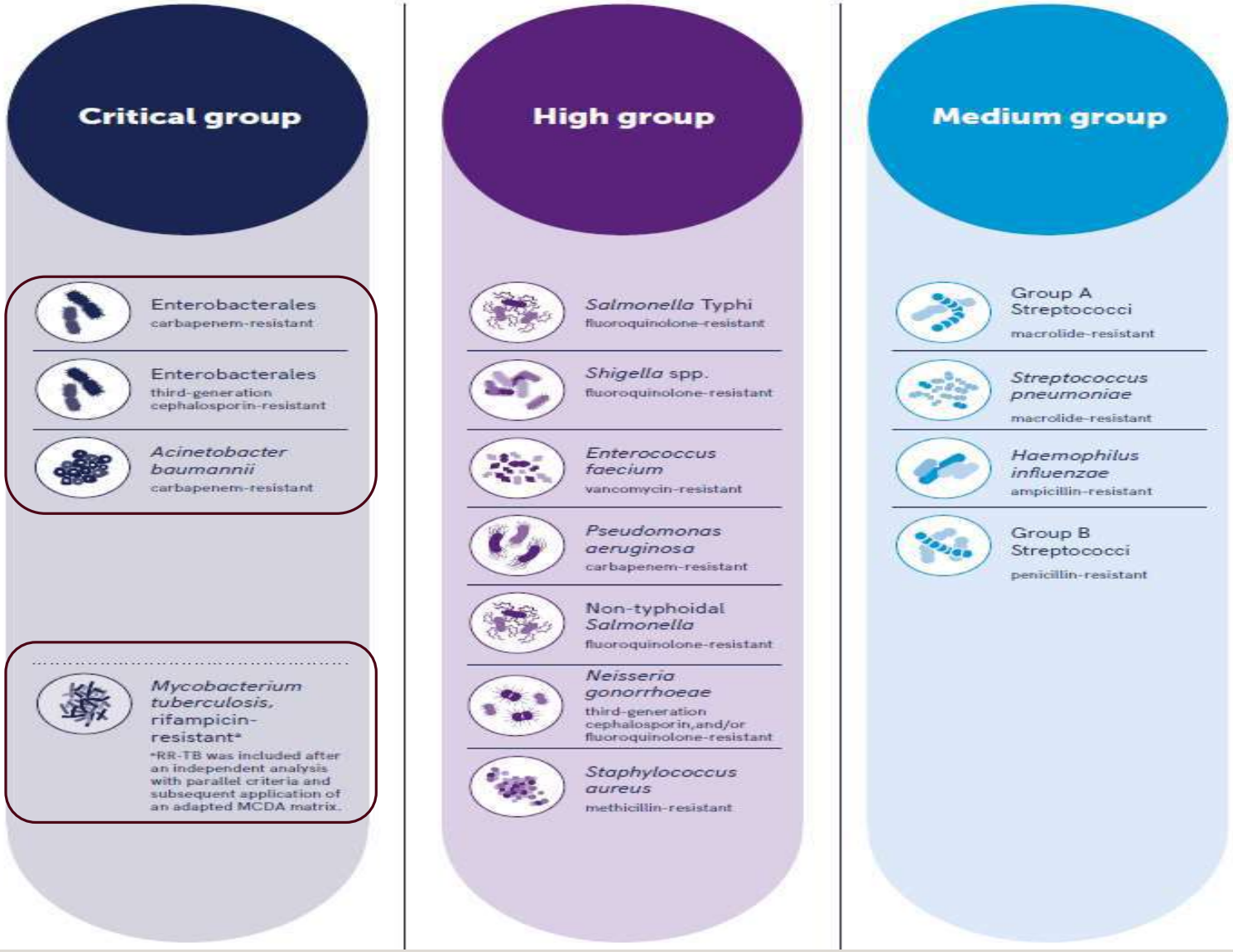
25/04/2025

WHO Bacterial Priority Pathogens List, 2024

Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance

Fig 4. WHO Bacterial Priority Pathogens List, 2024

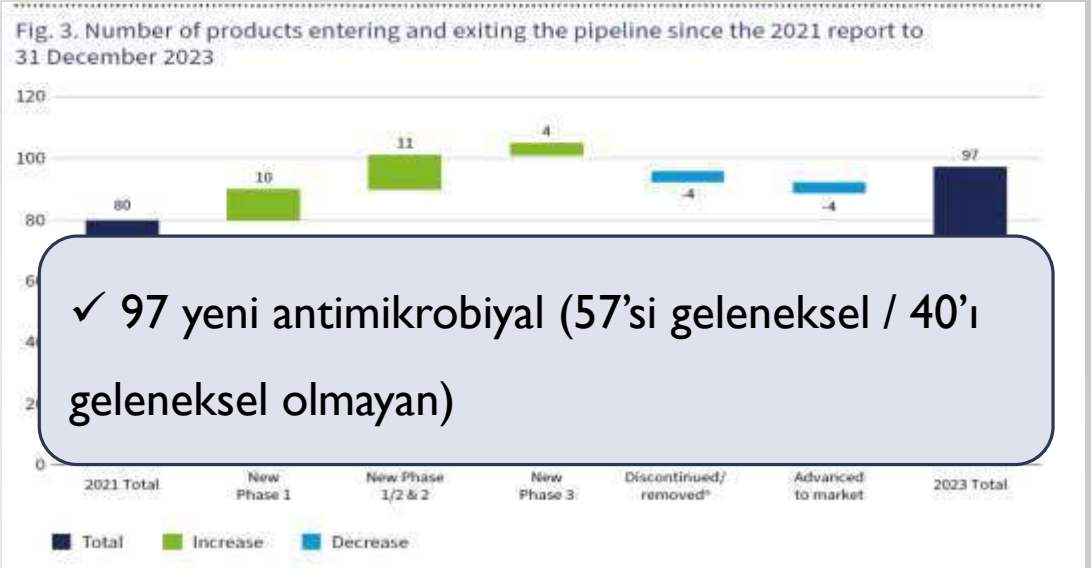


* https://www.who.int/publications/i/item/9789240093461

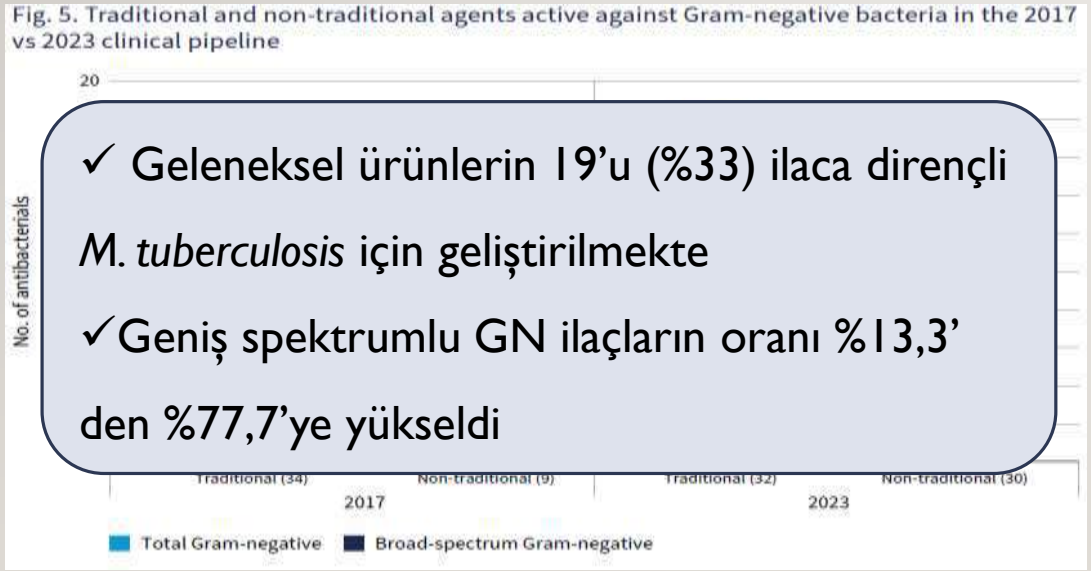
2023 Antibacterial agents in clinical and preclinical development

an overview and analysis

World Health Organization

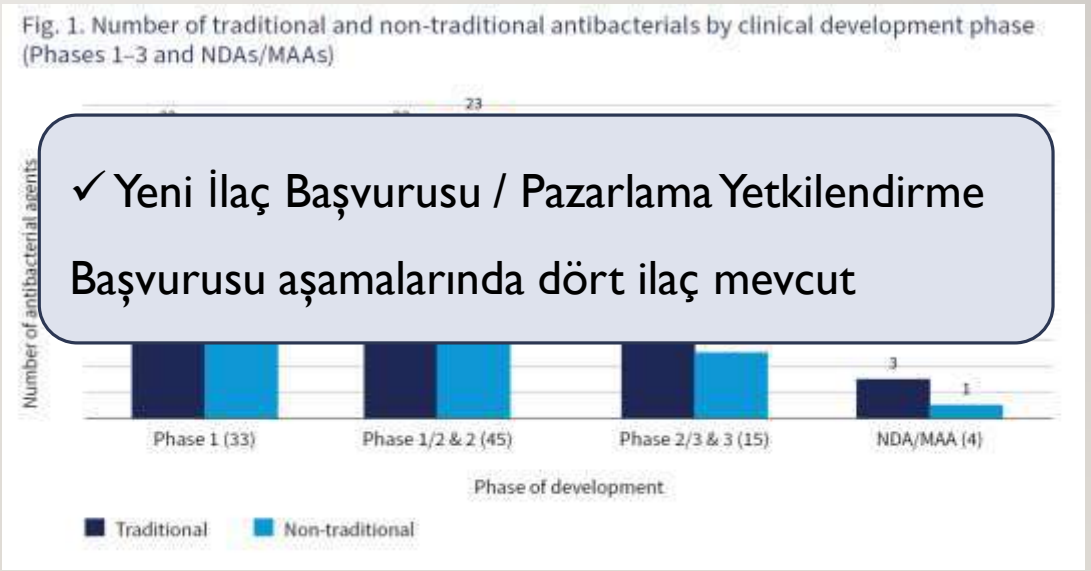


✓ 97 yeni antimikrobiyal (57'si geleneksel / 40'ı geleneksel olmayan)



✓ Geleneksel ürünlerin 19'u (%33) ilaca dirençli *M. tuberculosis* için geliştirilmekte

✓Geniş spektrumlu GN ilaçların oranı %13,3' den %77,7'ye yükseldi



✓Yeni İlaç Başvurusu / Pazarlama Yetkilendirme Başvurusu aşamalarında dört ilaç mevcut

* https://www.who.int/publications/i/item/9789240094000

Table 1a. Traditional antibacterial agents that gained market authorization between 1 July 2017 and 31 December 2023

Name (trade name USA/ EU)	Marketing authoriza-tion holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML and AWaRe classification*	Expected activity against priority pathogens			
							CRAB	CRPA	CRE	OPP
Sulbactam + durlobactam (Xacduro)	Innoviva (formerly Entasis Therapeutics)	FDA (05/2023)	BLI/PBP1,3 binder + DBO-PBP2 binder	iv	HABP/VABP	WHO EML: not yet evaluated; AWaRe: not yet classified	•	X	X	/
Delafloxacin (Baxdela/ Quofenix)	Melinta Therapeutics (USA) (Menarini, EU)	FDA (6/2017 ABSSSI, 10/2019 CAP), EMA (12/2019 ABSSSI, 02/2021 CAP)	Fluoroquinolone	DNA giraz ve topoizomeraz IV inh. **MRSA ✓ Anaerob ✓**						•
Meropenem + vaborbactam (Vabomere)	Melinta Therapeutics (USA) (Menarini, EU)	FDA (8/2017) EMA (11/2018)	β-lactam (carbapenem) + boronate BLI	iv	cUTI (cUTI, cIAI, HABP/VABP in EU)	WHO EML: yes; AWaRe: Reserve	X	X	•[b]	/
Plazomicin (Zemdri)	Achaogen (Cipla USA / QiLu Antibiotics, China)	FDA (8/2018)	Aminoglikozid dirençli **izolatların çoğuna etkili** ! **EMA başvurusu** mali gerekçeler nedeniyle 2020 yılında **geri çekildi !**							/
Eravacycline (Xerava)	Tetraphase Pharmaceuticals (La Jolla Pharmaceutical Company, Everest Medicines)	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	WHO EML: no; AWaRe: Reserve	?	X	•	/
Omadacycline (Nuzyra)	Gurnet Point Capital and Novo Holdings	FDA (10/2018)	Tetracycline	iv and PO	CABP (iv), ABSSSI (iv, PO)	WHO EML: no; AWaRe: Reserve	X	X	X	•

* https://www.who.int/publications/i/item/9789240094000

Name (trade name USA/ EU)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication(s)	WHO EML and AWaRe classification[a]	Expected activity against priority pathogens			
							CRAB	CRPA	CRE	OPP
Imipenem/ cilastatin (Recarbrio) + Relebactam	Merck Sharp & Dohme	FDA (7/2019 cUTI/cIAI, 7/2020 HAP/VAP), EMA (2/2020 G-ve)	β-Lactam (carbapenem) / degradation inhibitor + DBO-BLI	iv	cUTI, cIAI, HABP/ VABP	WHO EML: no; AWaRe: Reserve	X	?	•[b]	/
Lefamulin (Xenleta)	Nabriva (Sunovion Pharmaceuticals Canada)	FDA (8/2019) EMA (7/2020)	Pleuromutilin	Protein sentezi inhibisyonu (peptidil transferaz), **MRSA ✓ VRE ✓**						
Pretomanid (Dovprela)	TB Alliance (Viatris)	FDA (8/2019) EMA (8/2020) CDSCO (7/2020)	Nitroimidazole	PO	XDR-TB	WHO EML: yes; AWaRe: not yet classified	/	/	/	•[c]
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PDMA (8/2019)	Fluoroquinolone	DNA giraz ve topoizomeraz IV inh. **MRSA ✓ Anaerob ✓**						•
Cefiderocol (Fetroja)	Shionogi	FDA (11/2019 cUTI, 9/21 HAP/ VAP), EMA (4/2020)	Siderophore β-lactam (cephalosporin)	iv	cUTI, HABP/ VABP, aerobic G-negative[f]	WHO EML: yes; AWaRe: Reserve	•	•	•	/
Levonadiflox-acin (Emrok); alalevonadi-floxacin (Emrok-O)	Wockhardt	CDSCO (1/2020)	Fluoroquinolone	DNA giraz ve topoizomeraz IV inh. **MRSA ✓ Anaerob ✓**		WHO EML: not yet respectively[e]				•
Contezolid (Youxitai); contezolid acefosamil	MicuRx	NMPA (6/2021)	Oxazolidinone	Linezolid eş değeri; **seratoninerjik nörotoksisite** ve **myelosupresyon etkisi dah az !!**						•

* https://www.who.int/publications/i/item/9789240094000

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment	Expected activity against priority pathogens				
						CRAB	CRE	3GCRE	CRPA	OPP[a]
Solithromycin (T-4288)	NDA	Macrolide/ketolide								•
Cefepime + taniborbactam (VNRX-5133)	NDA	β-Lactam (cephalosporin) + boronate BLI	iv	Venatorx Pharmaceuticals/ GARDP/Everest Medicines		X	•	•	•	/
Cefepime (EXBLIFEP) + enmetazobactam (AAI-101)	FDA onaylı	ctam (cephalosporin) + BLI	iv	Allecra Therapeutics		X	X	•	X	/
Sulopenem; sulopenem etzadroxil/probenecid	FDA onaylı	ctam (thiopenem)	iv/PO	Iterum Therapeutics		X	X	•	X	/
Zoliflodacin	3	Spiropyrimider (topoisomeras	XDR *N.gonorrhea*	Innoviva (former Entasis Therapeutics)/ GARDP		/	/	/	/	•
Gepotidacin	FDA onaylı	aacenapht isomerase	XDR *N.gonorrhea*	GSK		/	/	?[c]	/	?
Nafithromycin (WCK-4873)	3	Macrolide/ketolide	PO	Wockhardt/ Jemincare		/	/	/	/	•
Cefepime + zidebactam (WCK 5222)[d]	3	β-Lactam (cephalosporin) + DBO-BLI/PBP2 binder	iv	Wockhardt		?[c]	•	•	?[c]	/
Cefepime + nacubactam (OP0595)[d]	3	β-Lactam (cephalosporin) + DBO-BLI/PBP2 binder	iv	Meiji Seika		/	•	•	?	/
Aztreonam + Nacubactam (OP0595)[d]	3	β-Lactam (monobactam) + DBO-BLI/PBP2 binder	iv	Meiji Seika		/	•	•	X	/

Hepatotoksisite ve üretim sorunlarına ilişkin endişe → FDA red (2016)

* https://www.who.int/publications/i/item/9789240094000

INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment
Funobactam (XNW4107) + imipenem + cilastatin	3	DBO-BLI + β-lactam (carbapenem) + degradation inhibitor	iv	Evopoint Bioscience	
Benapenem	2	β-Lactam (carbapenem)	iv	Xuanzhu Biopharm[j]	
Afabicin (Debio-1450)	2	Pyrido-enamide (FabI inhibitor)	iv/PO	Debiopharm	
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv/PO[k]	TenNor Therapeutics	
RECCE 327 (R327)	1, 2	Synthetic (acrolein) polymer	iv/to		
Murepavadin (POL7080, iMPV)	1, 2	Macrocyclic peptidomimetic compound	inhaled[l]	Spexis	
Meropenem + nacubactam (OP0595)[d]	1	β-Lactam (carbapenem) + DBO-BLI/PBP2 binder	iv	Meiji Seika	
Cefpodoxime proxetil + ETX0282[d]	1	β-Lactam (cephalosporin) + DBO-BLI/PBP2 binder	PO	Entasis Therapeutics	
Ceftibuten + ledaborbactam (VNRX-7145)	1	β-Lactam (cephalosporin) + boronate-BLI	PO	Venatorx Pharmaceuticals	
Xeruborbactam (QPX7728) + β-lactam (S-649228)	1	Boronate-BLI + undisclosed iv β-lactam	iv	Qpex Biopharma / Shionogi	

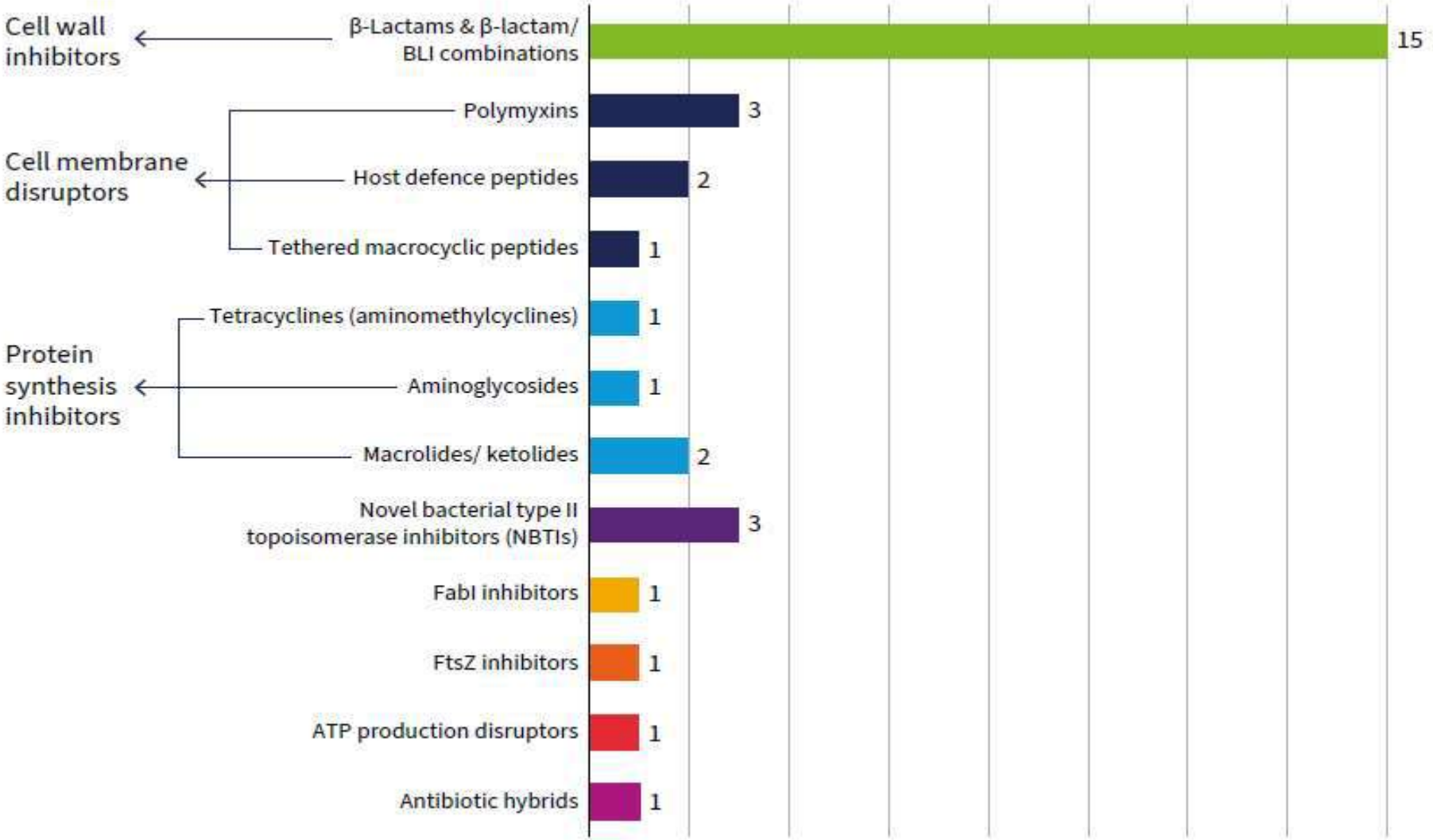
INN (company code)	Phase	Antibacterial class	Route of administration	Developer	Nonclinical data supporting the activity assessment
Upleganan (SPR-206)	1	Polymyxin	iv	Spero Therapeutics	
MRX-8	1	Polymyxin	iv	MicuRx	
QPX9003	1	Polymyxin	iv	Brii Biosciences	
Zifanocycline (KBP-7072)	1	Tetracycline (aminomethylcycline)	iv/PO	KBP BioSciences	
		Aminoglycoside	iv	Juvabis	
		Difluorobenzamide (FtsZ inhibitor)	iv/PO	TAXIS Pharmaceuticals	
Zosurabalpin (RG6006)	1	Macrocyclic peptide	iv	Roche	
BWC0977	1	Pyrazino-oxazinones; novel NBTI	iv/PO	Bugworks Research	
OMN6	1	Insect host defence peptide	iv	Omnix Medical	
Ertapenem + zidebactam[d]	1	β-Lactam (carbapenem) + DBO-BLI/PBP2 binder	iv	Wockhardt / NIAID	
Meropenem + ANT3310	1	β-Lactam (carbapenem) + DBO-BLI/PBP2 binder	iv	Antabio SAS	

Sefiderokol / Xeruborbaktam ?

* https://www.who.int/publications/i/item/9789240094000

* Hara, T., Ishibashi, N., Miyagawa, D., Onishi, M., Lomovskaya, O., & Yamano, Y. (2025). 514. The Impact of Xeruborbactam on *in vitro* Activity of Cefiderocol against a Panel of *Acinetobacter baumannii* Enriched in Isolates with Reduced Cefiderocol Susceptibility. *Open Forum Infectious Diseases*, *12*(Suppl 1), ofae631.166. https://doi.org/10.1093/ofid/ofae631.166

Fig. 10. Distribution of traditional agents according to their antibiotic class



* https://www.who.int/publications/i/item/9789240094000

➢ BETA-LAKTAM ANTİBİYOTİKLER

Sulopenem / Probenesid (Orlynvah®)

- İlk onaylanan oral penem'dir (Karbapenem → Prolin halkası, Penem → Tiazolin halkası)
- **ESBL + ve Amp C + Enterobacterales ✓**
- ***P. aeruginosa'ya*** ETKİSİZ !
- Sulopenem + Sefuroksim kombinasyonu *Mycobacterium abscessus'a* etkili ✓
- Oral biyoyararlanımı %20-34 → **+ Probenesid ile %62** (yemeklerle beraber kullanılmalı)
- 2 x 1 tablet, renal doz ayarı gerekmiyor, GFR<15'de önerilmiyor
- **Kan diskrazisi** olan ve **ürik asit böbrek taşı** olan kişilerde **K.E. !**
- FDA onayı 2024 (komplike olmayan İYE)

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

→ Çok merkezli, randomize, çift kör, faz 3 (SURE 1)

→ Komplike olmayan İYE → 3-5 gün tedavi (* %26,7'si siprofloksasin dirençli, %13,5 ESBL +)

→ Sulopenem 5 gün (n=833) vs. Siprofloksasin 3 gün (n=827)

→ Klinik iyileşme (5. gün) → Sulopenem → **%68,7** vs. Siprofloksasin → **%67,3**

→ Klinik kür + MB eradikasyon (12.gün)→ Sulopenem → **%65,6** vs. Siprofloksasin→ **%67,9**

*** Siprofloksasin duyarlı** izolatlarda → Sulopenem → **%66,8** vs. Siprofloksasin → **%78,6**

→ Tedavi ilişkili yan etki→ Sulopenem→ **%24,8 (%12,4 İSHAL!)** vs. Siprofloksasin→ **%13,9**

* İstenmeyen olay nedenli ilaç kesimi → Sulopenem → **%1,6** vs. Siprofloksasin → **%1,0**

* Dunne MW, Aronin SI, Das AF, et al. Sulopenem or Ciprofloxacin for the Treatment of Uncomplicated Urinary Tract Infections in Women: A Phase 3, Randomized Trial [published correction appears in Clin Infect Dis. 2023 Sep 18;77(6):937. doi: 10.1093/cid/ciad216.]. *Clin Infect Dis*. 2023;76(1):66-77. doi:10.1093/cid/ciac738

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

→ Çok merkezli, randomize, çift kör, faz 3 (SURE 2)

→ GNB ilişkili komplike İYE → 7-14 günlük tedavi (* %77,3'ü *E.coli*, %26,6 ESBL +)

→ Sulopenem iv + po (n=444) vs. Ertapenem + AMC/Siprofloksasin (n=440)

→ Klinik iyileşme (21. gün) → Sulopenem → **%89,4** vs. Ertapenem → **%88,4**

→ Klinik kür + MB eradikasyon (21. gün) → Sulopenem → **%67,8** vs. Ertapenem → **%73,9**

* **ESBL + patojenlerde** → Sulopenem → **%71,8** vs. Ertapenem → **%68,0**

* **Kinolon duyarlı patojenlerde** → Sulopenem → **%67,7** vs. **Siprofloksasin → %86,5 !!**

→ Tedavi ilişkili yan etki → Sulopenem → **%6,0** vs. Ertapenem → **%9,2**

* İstenmeyen olay nedenli ilaç kesimi → Sulopenem → **%0,4** vs. Ertapenem → **%0,6**

* Dunne MW, Aronin SI, Das AF, et al. Sulopenem for the Treatment of Complicated Urinary Tract Infections Including Pyelonephritis: A Phase 3, Randomized Trial. *Clin Infect Dis*. 2023;76(1):78-88. doi:10.1093/cid/ciac704

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

ORIGINAL ARTICLE · Volume 31, Issue 3, P396-401, March 2025 Download Full Issue

A phase 3 randomized trial of sulopenem vs. ertapenem in

→ Çok merkezli, randomize, çift kör, faz 3

→ Komplike İAİ → 7-10 günlük tedavi (* %58,5'i *E.coli,* %16,4'ü *B. fragilis)*

→ Sulopenem iv + po (n=249) vs. Ertapenem + AMC / Siprofloksasin + Metranidazol (n=265)

→ Klinik iyileşme (28. gün) → Sulopenem → **%81,9** vs. Ertapenem → **%87,9**

→ Tedavi ilişkili yan etki → Sulopenem → **%6,0** vs. Ertapenem → **%5,1**

* Dunne MW, Aronin SI, Das AF, et al. A phase 3 randomized trial of sulopenem vs. ertapenem in patients with complicated intra-abdominal infections. *Clin Microbiol Infect*. 2025;31(3):396-401. doi:10.1016/j.cmi.2024.10.025

Tebipenem Hbr

- Tebipenem/pivoksil hidrobromür (SPR994) oral yoldan alınabilen (%60) bir ön ilaçdır.
- **ESBL + ve Amp C + Enterobacterales ✓, *P. aeruginosa'ya* zayıf etkili ! ✓**
- Faz 3 → KİYE (n=868); Tebipenem (3x600 mg po) vs. Ertapenem (1x1 gr) → 7-14 gün
  - Klinik yanıt (17-21.gün): Tebipenem **%93,1** vs. Ertapenem **%93,6**
  - Klinik + MB yanıt : Tebipenem **%58,8** vs. Ertapenem **%61,6**
  - İlaç ilişkili yan etki: Tebipenem **%9,3** (*%5,7 ishal) vs. Ertapenem **%6,1**
  - İstenmeyen olay nedenli ilaç kesimi : Tebipenem **%0,1** vs. Ertapenem **%1,2**
- Haziran 2022'de **FDA** tarafından **RED** ! → Doğrulayıcı Faz-3 çalışması devam ediyor ..

* Eckburg PB, Muir L, Critchley IA, et al. Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection. *N Engl J Med.* 2022;386(14):1327-1338. doi:10.1056/NEJMoa2105462

Sefiderokol (Fetroja® / Fectroja®)

- Siderofor görevi gören ve hücre dışı demiri bağlayan modifiye edilmiş bir sefalosporindir.
- **XDR Enterobacterales, *P. aeruginosa* ve *A. baumannii* ✓**
- Sınıf A, **B,** C ve **D** beta-laktamazlara karşı etkili

  → Azalmış duyarlılık ve direnç bildirilmiştir !
- Gram-pozitif bakterilere ve **Anaeroblara etkisiz !**
- FDA onayı 2019-2021 (KİYE, VİP, NKP)
- EMA onayı 2020 (Aerobik GNB)

* Ong'uti, S.; Czech, M.; Robilotti, E.; Holubar, M. Cefiderocol: A New Cephalosporin Stratagem Against Multidrug-Resistant Gram-Negative Bacteria. Clin. Infect. Dis. **2022**, 74, 1303–1312.

* Poirel, L.; Ortiz de la Rosa, J.-M.; Sadek, M.; Nordmann, P. Impact of Acquired Broad-Spectrum -Lactamases on Susceptibility to Cefiderocol and Newly Developed -Lactam/-Lactamase Inhibitor Combinations in Escherichia coli and Pseudomonas aeruginosa. Antimicrob. Agents Chemother. 2022, 66, e00039-22.

THE LANCET
Infectious Diseases

→ Çok merkezli, açık etiketli, RKÇ, Faz 3 (CREDIBLE-CR)

→ Karbapenem Dirençli GNB → KİYE, NKP, KDİ/Sepsis

→ Sefiderokol ± 2.ilaç (n=101) vs. En iyi alternatif (n=49)

→ Klinik Başarı (7. gün)

- NKP → Sefiderokol **%50** vs. En iyi alternatif **%53**
- KDİ → Sefiderokol **%43** vs. En iyi alternatif **%43**
- KİYE * → Sefiderokol **%53** vs. En iyi alternatif **%20**

→ Mortalite (28 gün)→ **Sefiderokol %34 !!** vs. En iyi alternatif **%18**

- ***A.baumanii* dışında** Sefiderokol **%22** vs. En iyi alternatif **%22**
- **KİYE'** de Sefiderokol **%12** vs. En iyi alternatif **%40**
- **MBL üreten** suşlarda Sefiderokol **%29** vs. En iyi alternatif **%75**

* Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(2):226-240. doi:10.1016/S1473-3099(20)30796-9

THE LANCET
Infectious Diseases

COMMENT · Volume 21, Issue 2, P153-155, February 2021 Download Full Issue

- Karbapenem dirençli organizmaların neden olduğu infeksiyonların tedavisi için **açıkça yetersiz olan karşılaştırma ajanları kadar iyi** olduğudur
- **CRAB infeksiyonlarınının** tedavisinde kullanımı sadece diğer ilaçlara **direnç** gösterildiği durumlarla **sınırlandırılmalıdır.**
- Sefiderokol'a karşı **direncin ortaya çıkma sıklığı endişe vericidir** (%15'inde MİK'ler ≥4 kat artış)
- Sefiderokol, gram negatif dirence karşı verilen savaşlarda değerli bir asker olacak ancak muhtemelen savaşı kazanamayacak.

THE LANCET
Infectious Diseases

CORRESPONDENCE · Volume 21, Issue 5, P597-598, May 2021 Download Full Issue

Widespread cefiderocol heteroresistance in

	Acinetobacter	*Klebsiella*	*Pseudomonas*	*Stenotrophomonas*
CREDIBLE-CR trial[1]				
All-cause mortality*	49% (19/39)	21% (6/28)	18% (2/11)	67% (2/3)
Detected resistance†	3% (1/36)	0% (0/27)	0% (0/12)	0% (0/5)
SIDERO-CR study[5]				
Detected resistance	10% (38/368)	2% (12/720)	1% (2/262)	0% (0/217)
GA, USA, surveillance				
Detected resistance	8% (9/108)	6% (5/89)	0% (0/69)	0% (0/29)
Heteroresistance	59% (64/108)	30% (27/89)	9% (6/69)	48% (14/29)

All-cause mortality data are from the CREDIBLE-CR trial.[1] Detected resistance data (minimum inhibitory concentration >4 µg/mL) are from the CREDIBLE-CR trial[1] or SIDERO-CR study,[5] or were generated by disk diffusion assay on carbapenem-resistant isolates from GA, USA, according to Clinical and Laboratory Standards Institute guidance. Heteroresistance data were established by population analysis profile to identify minority

* Heil EL, Tamma PD. Cefiderocol: the Trojan horse has arrived but will Troy fall?. *Lancet Infect Dis*. 2021;21(2):153-155. doi:10.1016/S1473-3099(20)30828-8

* Choby JE, Ozturk T, Satola SW, Jacob JT, Weiss DS. Widespread cefiderocol heteroresistance in carbapenem-resistant Gram-negative pathogens. *Lancet Infect Dis*. 2021;21(5):597-598. doi:10.1016/S1473-3099(21)00194-8

Antimicrobial Agents and Chemotherapy

MECHANISMS OF RESISTANCE
August 2024 Volume 68 Issue 8 e00127-24
https://doi.org/10.1128/aac.00127-24

Cefiderocol heteroresistance associated with mutations in TonB-dependent receptor genes in *Pseudomonas aeruginosa* of clinical origin

Stephanie L. Egge [1,2,3], Samie A. Rizvi [1,2], Shelby R. Simar [4], Manuel Alcalde [5,6], Jose R. W. Martinez [5], Blake M. Hanson [4], An Q. Dinh [1,2], Rodrigo P. Baptista [1,2,7], Truc T. Tran [1,2,7], Samuel A. Shelburne [8], Jose M. Munita [5], Cesar A. Arias [1,2,7], Morgan Hakki [3], William R. Miller [1,2,7]

JAC-Antimicrobial Resistance
Education and research in antimicrobial stewardship and resistance

JAC Antimicrob Resist. 2024 Sep 9;6(5):dlae146. doi: 10.1093/jacamr/dlae146

Frequency of cefiderocol heteroresistance among patients treated with cefiderocol for carbapenem-resistant *Acinetobacter baumannii* infections

Ryan K Shields [1,2,3,✉], Ava J Dorazio [4], Giusy Tiseo [5], Kevin M Squires [6], Alessandro Leonildi [7], Cesira Giordano [8], Ellen G Kline [9], Simona Barnini [10], Alina Iovleva [11,12], Marissa P Griffith [13], Daria Van Tyne [14,15,16,✉], Yohei Doi [17,18,19], Marco Falcone [20]

Results: Overall, 59% of infecting CRAb isolates were identified as cefiderocol-heteroresistant; rates were higher among isolates from Italy (79%) than the USA (38%). The median Charlson Comorbidity and SOFA scores were 4 and 5, respectively; 44% of patients had pneumonia, which was the most common infection type. Rates of 28-day clinical success and survival were 30% and 73%, respectively. By broth microdilution, cefiderocol MICs ≥1 mg/L were associated with higher failure rates than MICs ≤0.5 mg/L (81% versus 55%). Rates of clinical failure were numerically higher among patients infected by cefiderocol-heteroresistant compared with susceptible CRAb (81% versus 55%). Whole-genome sequencing identified a premature stop codon in the TonB-dependent receptor gene *piuA* in six isolates, all of which were heteroresistant.

Conclusions: This pilot study supports the hypothesis that cefiderocol treatment failure may be associated with higher MICs and/or the presence of heteroresistance. Further studies are needed to confirm these findings.

* Egge SL, Rizvi SA, Simar SR, et al. Cefiderocol heteroresistance associated with mutations in TonB-dependent receptor genes in *Pseudomonas aeruginosa* of clinical origin. *Antimicrob Agents Chemother*. 2024;68(8):e0012724. doi:10.1128/aac.00127-

* Shields RK, Dorazio AJ, Tiseo G, et al. Frequency of cefiderocol heteroresistance among patients treated with cefiderocol for carbapenem-resistant *Acinetobacter baumannii* infections. *JAC Antimicrob Resist*. 2024;6(5):dlae146. Published 2024 Sep 9.

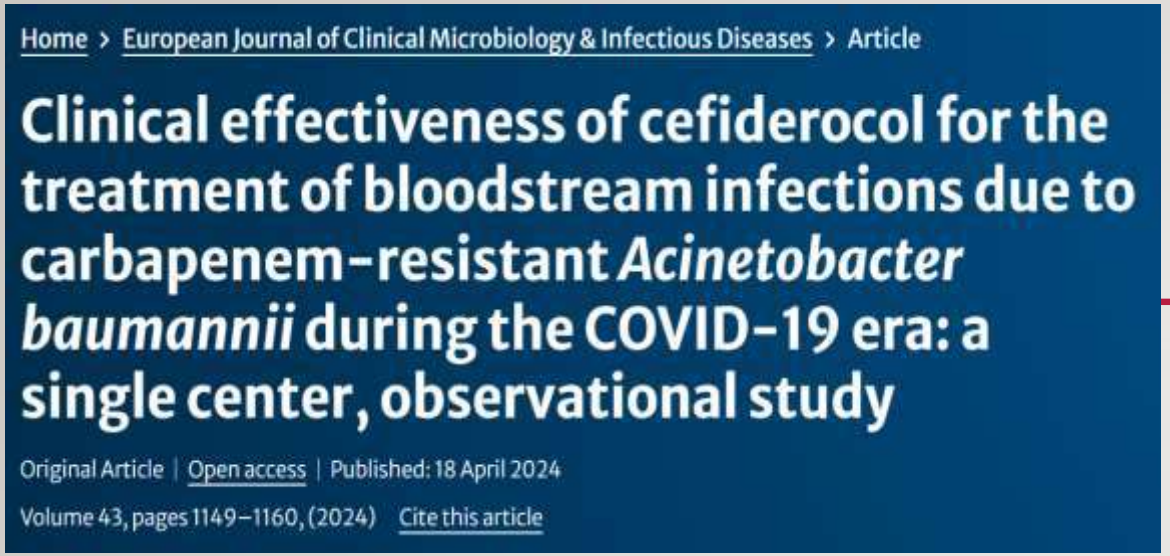
Table 2 In vitro activity of cefiderocol against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible			MβL producers				NDM producers		
				Enterobacterales	*P. aeruginosa*	*ACB*	Enterobacterales	*P. aeruginosa*	*ACB*	*S. maltophilia*	Enterobacterales	*P. aeruginosa*	*ACB*
[60]	Worldwide	2006–2023	CLSI	6638/7175;	4321/4389;	5560/6047;	1400/1679;	540/562;	74/93;	2922/3003;	1096/1476;	33/41;	66/85; 77.6%

Table 2 (continued)

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible			MβL producers				NDM producers		
				Enterobacterales	*P. aeruginosa*	*ACB*	Enterobacterales	*P. aeruginosa*	*ACB*	*S. maltophilia*	Enterobacterales	*P. aeruginosa*	*ACB*
[72]	Poland	2019–2022	EUCAST	60/60; 100%	-	-	60/60; 100%	-	-	-	60/60; 100%	-	-
[73]	Mexico	2012–2022	CLSI	-	-	-	-	-	-	96/101; 95%	-	-	-
[74]	Europe	2020	EUCAST	-	135/139; 97.1%	193/227; 85%	-	29/30; 96.7%	0/12; 0%	-	-	1/2; 50%	0/12; 0%
[75]	Northern Ireland, Spain and the Netherlands	-	EUCAST	-	-	-	-	-	-	88/102; 86.3%	-	-	-
[76]	Taiwan	2019–2021	CLSI	-	110/110; 100%	122/129; 94.6%	-	-	-	46/47; 97.9%	-	-	-
[77]	Italy	2019–2020	EUCAST	31/41; 75.6%	7/8; 87.5%	-	31/41; 75.6%	7/8; 87.5%	-	-	1/9; 11.1%	-	-
Pooled data		2006–2023	CLSI	7871/8503; 92.6%	5534/5618; 98.5%	5746/6258; 91.8%	2006/2315; 86.6%	1011/1037; 97.5%	97/128; 75.8%	3064/3151; 97.2%	1196/1594; 75%	46/56; 82.1%	78/109; 71.5%
			EUCAST	5288/6410; 82.5%	5309/5598; 94.8%	4569/5157; 88.6%	1504/2087; 72.1%	983/1042; 94.3%	72/140; 51.4%	3119/3144; 99.2%	627/1242; 50.5%	52/73; 71.2%	59/124; 47.6%

* Boattini M, Gaibani P, Comini S, et al. In vitro activity and resistance mechanisms of novel antimicrobial agents against metallo-β-lactamase producers. *Eur J Clin Microbiol Infect Dis*. Published online March 10, 2025. doi:10.1007/s10096-025-05080-1



→ Retrospektif kohort, CRAB KDİ

→ Sefiderokol (n=50) vs. Kolistin (n=54)

→ Klinik iyileşme → Sefiderokol **%66** vs. CT **%44,4**

→ Mortalite (14.gün)→ Sefiderokol **%22** vs. CT **%31**

→ Ciddi yan etki → Sefiderokol **%10** vs. CT **%38,8**

→ Sefiderokol; mortalite için bağımsız **prediktör değil**

→ 6 gözlemsel çalışma

→ Sefiderokol (n=251) vs. Kolistin (n=372)

→ Sefiderokol ile **tüm nedenlere bağlı ölüm daha az** (**RR=0.71**, 95% CI: 0.54– 0.92, p=0.01).

-KDİ (RR=0.61, 95% CI: 0.41– 0.90, P=0.01)

- VİP (RR=0.62, 95% CI: 0.33–1.17, P=0.14)

* Oliva, A., Liguori, L., Govino, S. *et al.* Clinical effectiveness of cefiderocol for the treatment of bloodstream infections due to carbapenem-resistant *Acinetobacter baumannii* during the COVID-19 era: a single center, observational study. *Eur J Clin Microbiol Infect Dis* **43**, 1149–1160 (2024).

* Zhan Y, Mao W, Zhao C, et al. Comparison of cefiderocol and colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii: a systematic review with meta-analysis and trial sequential analysis [published correction appears in BMC Infect Dis. 2024 Oct 1;24(1):1086. doi: 10.1186/s12879-024-09979-6.]. *BMC*

Fetroja dosing for most patients: q8h IV infusion

Recommended dosage and dosage adjustments of Fetroja for adult patients

ESTIMATED CREATININE CLEARANCE (CLcr)[a]	DOSE	FREQUENCY
≥120 mL/min (Patients with augmented renal clearance)	2 grams	Every 6 hours
60 to 119 mL/min (Recommended dosage)	2 grams	Every 8 hours
30 to 59 mL/min	1.5 grams	Every 8 hours
15 to 29 mL/min	1 gram	Every 8 hours
<15 mL/min (Patients with or without intermittent HD[b])	0.75 gram	Every 12 hours

* https://www.shionogi.com/content/dam/shionogi/si/products/pdf/fetroja.pdf

Yeni Beta-laktamaz inhibitörleri

Siklik boronatlar

- Vaborbaktam (A, D)
- **Taniborbaktam (A, B, D)**
- **Xeruborbaktam (A, B, D)**

Beta-laktamaz inhibitörleri

- Avibaktam (A, D)
- Relebaktam (A, D)
- Durlobaktam (A, D)
- Enmetazobaktam (-)
- **Zidebaktam (B, D)**
- **Nakubaktam (B, D)**
- Funobaktam (A, D)
- Pralurbaktam (A, D)

* Outeda-García M, Arca-Suárez J, Lence E, et al. Advancements in the fight against globally distributed OXA-48 carbapenemase: evaluating the new generation of carbapenemase inhibitors. *Antimicrob Agents Chemother*. 2025;69(2):e0161424. doi:10.1128/aac.01614-24

* Katsarou A, Stathopoulos P, Tzvetanova ID, Asimotou CM, Falagas ME. β-Lactam/β-Lactamase Inhibitor Combination Antibiotics Under Development. *Pathogens*. 2025;14(2):168. Published 2025 Feb 8. doi:10.3390/pathogens14020168

Sulbaktam-Durlobaktam (Xacduro ®)

- Durlobaktam; A, C ve **D** serin beta-laktamaz sınıflarını etkili bir şekilde inhibe eden yeni bir diazabisiklooktan beta-laktamaz inhibitörüdür.

  → Sulbaktam PBP 1 ve 3'e, Durlobaktam PBP 2'ye bağlanır

  → Tek başına verildiğinde *A. baumannii*'ye karşı etkisizdir !

  → Durlobaktam PBP 2 ile **Enterobacterales'e karşı** aktivite gösterir iken

  - **XDR *A. baumannii* ✓**
  - **Metallo-beta-laktamazlara etkisiz**
  - FDA onayı 2023 (***A.baumanii*** ilişkili VİP, NKP)

* FDA approves new treatment for pneumonia caused by certain difficult-to-treat bacteria. In: FDA/press announcements [website]. Silver Spring (MD): US Food and Drug Administration; 2023 (https://www.fda.gov/ news-events/press-announcements/fda-approvesnew- treatment-

*Karvouniaris M, Almyroudi MP, Abdul-Aziz MH, et al. Novel Antimicrobial Agents for Gram-Negative Pathogens. *Antibiotics (Basel)*. 2023;12(4):761. Published 2023 Apr 16. doi:10.3390/antibiotics12040761

THE LANCET
Infectious Diseases

ARTICLES · Volume 23, Issue 9, P1072-1084, September 2023

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→ Çok merkezli, randomize, aktif kontrollü, faz 3, noinferiority klinik çalışması (ATTACK)

→ CRABC ilişkili NKP, VİP, KDİ

→ Sulbaktam-Durlobaktam + İmipenem (n=63) vs. Kolistin + İmipenem (n=62)

→ Klinik iyileşme (7. gün) → SUL-DUR → **%61,9** vs. Kolistin → **%40**

→ 28 günlük mortalite → SUL-DUR → **%19** vs. Kolistin → **%32**

→ Nefrotoksisite → SUL-DUR → **%13,2** vs. Kolistin → **%27,6**

* Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of sulbactam-durlobactam versus colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii-calcoaceticus complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK). *Lancet Infect Dis*. 2023;23(9):1072-1084. doi:10.1016/S1473-3099(23)00184-6

JOURNAL ARTICLE

Successful Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Meningitis With Sulbactam-Durlobactam

Get access

Pranita D Tamma ✉, Shanan Immel, Sara M Karaba, Caitlin L Soto, Rick Conzemius, Emily Gisriel, Tsigereda Tekle, Haley Stambaugh, Emily Johnson, Jeffrey A Tornheim ... Show more

Clinical Infectious Diseases, Volume 79, Issue 4, 15 October 2024, Pages 819–825, https://doi.org/10.1093/cid/ciae210

Published: 17 April 2024 **Article history** ▾

Methods

We report the case of a 42-year-old woman with CRAB meningitis who experienced persistently positive cerebrospinal fluid (CSF) cultures for 13 days despite treatment with high-dose ampicillin-sulbactam and cefiderocol. On day 13, she was transitioned to sulbactam-durlobactam and meropenem; 4 subsequent CSF cultures remained negative. After 14 days of sulbactam-durlobactam, she was cured of infection. Whole genome sequencing investigations identified putative mechanisms that contributed to the reduced cefiderocol susceptibility observed during cefiderocol therapy. Blood and CSF samples were collected pre-dose and 3-hours post initiation of a sulbactam-durlobactam infusion.

Antimicrobial Chemotherapy | Brief Report | 30 January 2024

In vitro activity of sulbactam-durlobactam against colistin-resistant and/or cefiderocol-non-susceptible, carbapenem-resistant *Acinetobacter baumannii* collected in U.S. hospitals

Authors: Alina Iovleva, Christi L. McElheny, Erin L. Fowler, Eric Cober, Erica S. Herc, Cesar A. Arias, Carol Hill, SHOW ALL (15 AUTHORS), Yohei Doi AUTHORS INFO & AFFILIATIONS

https://doi.org/10.1128/aac.01258-23 · Check for updates

Abstract

The activity of a novel β-lactamase inhibitor combination, sulbactam-durlobactam (SUL-DUR), was tested against 87 colistin-resistant and/or cefiderocol-non-susceptible carbapenem-resistant *Acinetobacter baumannii* clinical isolates collected from U.S. hospitals between 2017 and 2019. Among them, 89% and 97% were susceptible to SUL-DUR and imipenem plus SUL-DUR, with MIC_{50}/MIC_{90} values of 2 µg/mL/8 µg/mL and 1 µg/mL/4 µg/mL, respectively. The presence of amino acid substitutions in penicillin-binding protein 3, including previously reported A515V or T526S, was associated with SUL-DUR non-susceptibility.

Keywords: antimicrobial resistance; diazabicyclooctane; surveillance.

* Tamma PD, Immel S, Karaba SM, et al. Successful Treatment of Carbapenem-Resistant Acinetobacter baumannii Meningitis With Sulbactam-Durlobactam. *Clin Infect Dis*. 2024;79(4):819-825. doi:10.1093/cid/ciae210

* Iovleva A, McElheny CL, Fowler EL, et al. *In vitro* activity of sulbactam-durlobactam against colistin-resistant and/or cefiderocol-non-susceptible, carbapenem-resistant *Acinetobacter baumannii* collected in U.S. hospitals. *Antimicrob Agents Chemother*. 2024;68(3):e0125823.

Table 1: Dosage of XACDURO (Sulbactam and Durlobactam) in Patients (18 Years of Age and Older) Based on Renal Function

Dose of Sulbactam and Durlobactam (g)	Estimated CLcr (mL/min)*	Frequency
sulbactam 1 g and durlobactam 1 g	Greater than or equal to 130	Every 4 hours
	45 to 129	Every 6 hours
	30 to 44	Every 8 hours
	15 to 29	Every 12 hours
	less than 15†	For patients initiating XACDURO: Every 12 hours for the first 3 doses (0, 12, and 24 hours), followed by every 24 hours after the third dose† For patients currently receiving XACDURO whose CLcr declines to less than 15 mL/min: Every 24 hours

*CLcr = creatinine clearance estimated by Cockcroft-Gault equation

†For patients on hemodialysis, the dose should be administered after the dialysis session has ended

Sefepim / Enmetazobaktam (Exblifep®)

- Tazobaktam'ın triazol halkasına bir metil grubu eklenerek beta-laktamazlara karşı aktivitesi artmıştır.
- **ESBL+ Enterobacterales** ve ***P. aeruginosa*** ✓
- C sınıfı –laktamazı orta, D sınıfı OXA-10 ve OXA-48'i zayıf inhibe ederken **MBL'lere etkisizdir!**
- ***A. baumannii, S. maltophilia'ya*** ETKİSİZ !
- FDA onayı 2024 (KİYE)
- EMA onayı 2024 (KİYE, NKP, VİP, KDİ)

Clinical Trial > JAMA. 2022 Oct 4;328(13):1304-1314. doi: 10.1001/jama.2022.17034.

→ Çok merkezli, randomize, çift kör, non-inferiorty, faz 3 (ALLIUM)

→ GNB ilişkili komplike İYE → 7-14 günlük tedavi

* %95,6'sı Enterobacterales, %20,9 ESBL +

→ Sefepim / Enmetazobaktam (n=520) vs. Piperasilin / Tazobaktam (n=521)

→ Klinik iyileşme (14.gün) → CEF/ENME → **%92,5** vs. TZP → **%88,9**

→ Klinik kür + MB eradikasyon (14.gün) → CEF/ENME → **%79,1** vs. TZP → **%58,9**

*** ESBL + patojenlerde** → CEF/ENME → **%73,7** vs. TZP → **%51,5**

→ Tedavi ilişkili yan etki → CEF/ENME → **%19,8** vs. TZP → **%14,5**

* İstenmeyen olay nedenli ilaç kesimi → CEF/ENME → **%1,7** vs. TZP → **%0,8**

* Kaye KS, Belley A, Barth P, et al. Effect of Cefepime/Enmetazobactam vs Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients With Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA*. 2022;328(13):1304-1314. doi:10.1001/jama.2022.17034

Table 1: Recommended dose of EXBLIFEP in patients with renal impairment

Absolute eGFR (mL/min)	Recommended dose regimen for EXBLIFEP (cefepime and enmetazobactam)	Dosing interval
Mild (60 - <90)	cefepime 2 g and enmetazobactam 0.5 g	Every 8 hours
Moderate (30- <60)	cefepime 1 g and enmetazobactam 0.25 g	Every 8 hours
Severe (15- <30)	cefepime 1 g and enmetazobactam 0.25 g	Every 12 hours
End stage renal disease (<15)	cefepime 1 g and enmetazobactam 0.25 g	Every 24 hours
Patients requiring hemodialysis	cefepime 1 g and enmetazobactam 0.25 g loading dose on the first day of therapy and cefepime 0.5g and enmetazobactam 0.125 g thereafter (every 24 hours but after the haemodialysis session on haemodialysis days).	Every 24 hours
Patients undergoing continuous ambulatory peritoneal dialysis (CAPD)	cefepime 2 g and enmetazobactam 0.5 g	Every 48 hours

Aztreonam-Avibaktam (Emblaveo®)

- İlk monobaktam / beta-laktamaz inhibitörü kombinasyonu
- **XDR Enterobacterales ve *S. maltophilia* ✓**
- Sınıf A, **B,** C ve **D** beta-laktamazlara karşı etkili

  → **MBL + *P. aeruginosa'ya* kısmen etkili**

- ***A. baumannii'ye*** etkisiz!
- FDA onayı 2025 (KİAİ)
- EMA onayı 2024 (KİAİ, KİYE, VİP, NKP ve Aerobik GNB)

THE LANCET
Infectious Diseases

ARTICLES · Volume 25, Issue 2, P218-230, February 2025

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→ Çok merkezli, randomize, açık etiketli, faz 3 (REVİSİT)

→ GNB ilişkili KİAİ, NKP, VİP → 5-14 günlük tedavi

* %93'ü Enterobacterales, %24 karbapenemaz pozitif

→ Aztreonam-avibaktam ± Metranidazol (n=282) vs. Meropenem ± Kolistin (n=140)

→ Klinik iyileşme (28. gün) → ATM-AVI → **%68,4** vs. Meropenem → **%65,7**

→ 28 günlük mortalite ATM-AVI → **%4** vs. Meropenem → **%7**

* NKP / VİP → ATM-AVI → **%11** vs. Meropenem → **%19**

* Carmeli Y, Cisneros JM, Paul M, et al. Aztreonam-avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, multinational, open-label, phase 3, randomised trial. *Lancet Infect Dis*. 2025;25(2):218-230. doi:10.1016/S1473-3099(24)00499-7

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible		MβL producers		NDM producers	
				Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*
[48]	China	2021	CLSI	298/306; 97.4%	71/138; 51.4%	99/102; 97%	8/15; 53.3%	-	-
			EUCAST	298/306; 97.4%	97/138; 70.3%	99/102; 97%	11/15; 73.3%	-	-
[63]	Swiss	2022–23	EUCAST	-	34/39; 87.2%	-	34/39; 87.2%	-	-
			CLSI	-	16/39; 41%	-	16/39; 41%	-	-
[53]	USA	2019–21	CLSI/ EUCAST	258/261; 98.8%	-	32/33; 97%	-	28/29; 96.5%	-
[56]	Worldwide	2020–22	CLSI/ EUCAST	1011/1016; 99.5%	-	356/356; 100%	-	-	-
[58]	Worldwide	2016–2020	CLSI/ EUCAST	82,642/82.785; 99.8%	-	1681/1707; 98.5%	-	1395/1421; 98.2%	-
[69]	Taiwan	2013–2021	CLSI/ EUCAST	189/195; 96.9%	-	137/143; 95.8%	-	69/74; 93.2%	-
[71]	Europe	2020	EUCAST/ CLSI	140/148; 94.6%	-	35/35; 100%	-	27/27; 100%	-
[74]	Europe	2020	EUCAST	-	58/139; 41.7%	-	22/30; 73.3%	-	1/2, 50%
			CLSI	-	17/139; 12.2%	-	9/30; 30%		1/2, 50%
[76]	Taiwan	2019–2021	CLSI	-	14/110; 12.7%	-	-	-	-
			EUCAST	-	44/110; 40%	-	-	-	-
[90]	Spain	2018	CLSI/ EUCAST	54/55; 98.2%	-	54/55; 98.2%	-	9/10; 90%	-
[91]	China	2019	CLSI/ EUCAST	110/119; 92.4%	-	35/44; 79.5%	-	32/41; 78%	
[92]	UK	2015, 2017, 2019	CLSI/ EUCAST	413/464; 89%	-	413/464; 89%	-	193/243; 79.4%	-
[93]	Europe	2019–2020	CLSI/ EUCAST	421/424; 99.3%	-	109/109; 100%	-	81/81; 100%	-
[94]	Worldwide	2016–2017	CLSI/ EUCAST	582/583; 99.8%	-	114/114; 100%	-	-	-
[95]	China	2016–2017	CLSI/ EUCAST	161/161; 100%	-	161/161; 100%	-	151/151; 100%	-
[96]	Worldwide	2012–2015	EUCAST	1378/1498; 92%	-	249/267; 93.2%	319/452; 70.6%	-	-
			CLSI	1378/1498; 92%	8692/11842; 73.4%	249/267; 93.2%	280/452; 61.9%	-	-
[97]	Worldwide	2012–2013	EUCAST	537/577; 93.1%	3246/3766; 86.2%	91/91; 100%	88/118; 74.6%	-	-
			CLSI	537/577; 93.1%	2772/3766; 73.6%	91/91; 100%	52/118; 44.1%	-	-
Pooled data		2012–2023	EUCAST	88,196/88592; 99.5%	3479/4192; 83%	3566/3681; 96.9%	474/654; 72.5%	1985/2077; 95.6%	1/2; 50%
			CLSI	88,196/88592; 99.5%	11,582/16034; 72.2%	3566/3681; 96.9%	365/654; 55.8%	1985/2077; 95.6%	1/2; 50%

* Boattini M, Gaibani P, Comini S, et al. In vitro activity and resistance mechanisms of novel antimicrobial agents against metallo-β-lactamase producers. *Eur J Clin Microbiol Infect Dis*. Published online March 10, 2025. doi:10.1007/s10096-025-05080-1

Table 1. Recommended intravenous dose by type of infection in adult patients with CrCL[a] > 50 mL/min

Type of infection	Dose of aztreonam-avibactam		Infusion time	Dosing interval	Duration of treatment
	Loading	Maintenance			
cIAI[b]	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	5-10 days
HAP, including VAP	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	7-14 days
cUTI, including pyelonephritis	2 g/0.67 g	1.5 g/0.5 g	3 hours	Every 6 hours	5-10 days

Table 2. Recommended doses for patients with estimated CrCL ≤ 50 mL/min

Estimated CrCL (mL/min)[a]	Dose of aztreonam-avibactam[b]		Infusion time	Dosing interval
	Loading	Maintenance		
> 30 to ≤ 50	2 g/0.67 g	0.75 g/0.25 g	3 hours	Every 6 hours
> 15 to ≤ 30	1.35 g/0.45 g	0.675 g/0.225 g	3 hours	Every 8 hours
≤ 15 mL/min, on intermittent haemodialysis[c,d]	1 g/0.33 g	0.675 g/0.225 g	3 hours	Every 12 hours

* https://ec.europa.eu/health/documents/community-register/2024/20240422162367/anx_162367_en.pdf

Sefepim / Taniborbaktam

- Taniborbaktam; Vaborbaktama yapısal olarak benzeyen, daha geniş bir inhibisyon spektrumuna sahip bir borik asit beta-laktamaz inhibitörüdür
- **XDR Enterobacterales, *P. aeruginosa* ve *S. maltophilia* ✓**
- Sınıf A, **B** (**IMP ve bazı NDM'ler hariç**), C ve **D** beta-laktamazlara karşı etkili
- ***A. baumannii'ye*** ETKİSİZ !
- FDA onayı beklemede (02/2024 'de ilaç, test yöntemleri ve üretim süreci hakkında ek bilgiler talep edildi)
- 2. Faz 3 çalışması (CERTAIN-2) devam ediyor (VIP/NKP)

→ Çok merkezli, randomize, çift kör, aktif kontrollü, faz 3 (CERTAIN-1)

→ GNB ilişkili komplike İYE → 7-14 günlük tedavi

* %95,9'u Enterobacterales, %24,3 ESBL +

→ Sefepim / Taniborbaktam (n=293) vs. Meropenem (n=143)

→ Klinik iyileşme (19-23. gün) → FEP/TAN → **%85,7** vs. MEM → **%81,1**

→ Klinik kür + MB eradikasyon (19-23. gün) → FEP/TAN → **%70,6** vs. MEM → **%58,0**

*** ESBL + patojenlerde** → FEP/TAN → **%73,3** vs. MEM → **%55,0**

→ Tedavi ilişkili yan etki → FEP/TAN → **%13,4** vs. MEM → **%8,8**

* İstenmeyen olay nedenli ilaç kesimi → FEP/TAN → **%3,0** vs. MEM → **%0,9**

* Wagenlehner FM, Gasink LB, McGovern PC, et al. Cefepime-Taniborbactam in Complicated Urinary Tract Infection. *N Engl J Med*. 2024;390(7):611-622. doi:10.1056/NEJMoa2304748

* Moeck G, Gasink LB, Mendes RE, et al. Patient outcomes by baseline pathogen resistance phenotype and genotype in CERTAIN-1, a Phase 3 study of cefepime-taniborbactam versus meropenem in adults with complicated urinary tract infection. *Antimicrob Agents Chemother*. 2024;68(7):e0023624. doi:10.1128/aac.00236-24

Reference	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible and/or carbapenemase-producers		MβL producers		NDM producers		VIM producers		IMP producers
				Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales	*P. aeruginosa*	Enterobacterales
			CLSI	61/97; 62.9%	46/100; 46%	61/97; 62.9%	46/100; 46%	-	-	-	-	-
			Provisional BP	89/97	89/100; 89%	89/97	89/100	-	-	-	-	-
128]	Spain	2018	EUCAST	388/400	-	48/56; 85.7%	-	6/10; 60%	-	40/42; 95.2%	-	2/4; 50%
			CLSI	360/400; 90%	-	42/56; 75%	-	5/10; 50%	-	37/42; 88.1%	-	0/4; 0%
			Provisional BP	398/400	-	54/56; 96.4%	-	9/10; 90%		41/42; 97.6%		4/4; 100%
129]	Spain	2020	EUCAST	229/247; 92.7%	115/170; 67.6%	38/45; 84.4%	25/53; 47.2%	2/4; 50%	-	36/39; 92.3%	25/45; 55.5%	0/2; 0%
			CLSI	207/247; 83.8%	115/170; 67.6%	34/45; 77.8%	25/53; 47.2%	0/4; 0%	-	34/39; 87.2%	25/45; 55.5%	0/2; 0%
			Provisional BP	245/247	147/170; 86.5%	43/45; 95.5%	35/53; 66%	4/4; 100%	-	38/39; 97.4%	35/45; 77.8%	1/2; 50%
130]	India	2019–2021	EUCAST	209/570	-	14/250; 5.6%	-	14/250; 5.6%	-	-	-	-
			CLSI	172/570; 30.2%	-	12/250; 4.8%	-	12/250; 4.8%	-	-	-	-
			Provisional BP	338/570	-	70/250; 28%	-	70/250; 28%	-	-	-	-
Pooled data		2005–2023	EUCAST	2044/2693; 75.9%	475/750; 63.3%	560/1038; 53.9%	239/410; 58.3%	329/758; 43.4%	0/6; 0%	146/158; 92.4%	172/253; 68%	5/19; 26.3%
			CLSI	1798/2693; 66.8%	475/750; 63.3%	487/1035; 47%	239/410; 58.3%	276/758; 36.4%	0/6; 0%	138/158; 87.3%	172/253; 68%	0/19; 0%
			Provisional BP	2336/2693; 86.7%	615/750; 82%	748/1035; 72.3%	317/410; 77.3%	486/758; 64.1%	0/6; 0%	156/158; 98.7%	206/253; 81.4%	14/19; 73.7%

* Boattini M, Gaibani P, Comini S, et al. In vitro activity and resistance mechanisms of novel antimicrobial agents against metallo-β-lactamase producers. *Eur J Clin Microbiol Infect Dis*. Published online March 10, 2025. doi:10.1007/s10096-025-05080-1

THE LANCET
Infectious Diseases

CORRESPONDENCE · Volume 23, Issue 8, E277-E278, August 2023 Download Full Issue

Heteroresistance to cefepime–taniborbactam in metallo-β-lactamase-encoding Enterobacterales

Carter Abbott [a,b,c] · Sarah W Satola [a,c,d] · David S Weiss [a,b,c]

Affiliations & Notes Article Info

	Population analysis profile			Broth microdilution	
	Susceptible	Heteroresistant	Resistant	Susceptible	Resistant
NDM (n=29)	3·6% (1)	82·8% (24)	13·8% (4)	65·5% (19)	34·5% (10)
VIM (n=5)	0% (0)	100% (5)	0% (0)	100% (5)	0% (0)

- CDC ve FDA Antibiyotik Direnci İzolat Bankası'ndan MBL+ 34 suş (%70 NDM-1) popülasyon analizi profili kullanarak araştırıldı.
- Bu sonuçlar; MBL kodlayan Enterobacterales arasında sefepim-taniborbaktama karşı heterodirencin endişe verici bir şekilde sık görüldüğününü ortaya koymakta ve bu durumun klinik sonuçlar üzerindeki potansiyel etkisi bilinmemektedir.

* Abbott C, Satola SW, Weiss DS. Heteroresistance to cefepime-taniborbactam in metallo-β-lactamase-encoding Enterobacterales. *Lancet Infect Dis*. 2023;23(8):e277-e278. doi:10.1016/S1473-3099(23)00426-7

J Antimicrob Chemother 2023; **78**: 1191–1194
https://doi.org/10.1093/jac/dkad061 Advance Access publication 15 March 2023

Journal of Antimicrobial Chemotherapy

In vitro activity of cefepime/zidebactam and cefepime/taniborbactam against aztreonam/avibactam-resistant NDM-like-producing *Escherichia coli* clinical isolates

Christophe Le Terrier [1,2], Patrice Nordmann[1,3,4], Mustafa Sadek [1,5] and Laurent Poirel [1,3]*

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Background: Aztreonam/avibactam is one of the last therapeutic options for treating infections caused by NDM-like-producing Enterobacterales. However, PBP3-modified and NDM-producing *Escherichia coli* strains that co-produce CMY-42 have been shown to be resistant to this drug combination. The aim of our study was to assess the *in vitro* activity of cefepime/taniborbactam and cefepime/zidebactam against such aztreonam/avibactam-resistant *E. coli* strains.

Methods: MIC values of aztreonam, aztreonam/avibactam, cefepime, cefepime/taniborbactam, cefepime/zidebactam and zidebactam alone were determined for 28 clinical aztreonam/avibactam-resistant *E. coli* isolates. Those isolates produced either NDM-5 ($n=24$), NDM-4 ($n=2$) or NDM-1 ($n=2$), and they all co-produced CMY-42 ($n=28$). They all harboured a four amino acid insertion in PBP-3 (Tyr-Arg-Ile-Asn or Tyr-Arg-Ile-Lys).

Results: All strains were resistant to aztreonam/avibactam and cefepime, as expected. The resistance rate to cefepime/taniborbactam was 100%, with MIC_{50} and MIC_{90} being at 16 mg/L and 64 mg/L, respectively. Conversely, all strains were susceptible to cefepime/zidebactam, with both MIC_{50} and MIC_{90} at 0.25 mg/L. Notably, all strains showed low MICs for zidebactam alone, with MIC_{50} and MIC_{90} at 0.5 mg/L and 1 mg/L.

Conclusions: Our data highlighted the excellent *in vitro* performance of the newly developed β-lactam/β-lactamase inhibitor combination cefepime/zidebactam against aztreonam/avibactam-resistant *E. coli* strains, suggesting that this combination could be considered as an efficient therapeutic option in this context. Our study also highlights the cross-resistance between acquired resistance to aztreonam/avibactam and the cefepime/taniborbactam combination.

* Le Terrier C, Nordmann P, Sadek M, Poirel L. In vitro activity of cefepime/zidebactam and cefepime/taniborbactam against aztreonam/avibactam-resistant NDM-like-producing Escherichia coli clinical isolates. *J Antimicrob Chemother*. 2023;78(5):1191-1194. doi:10.1093/jac/dkad061

Sefepim / Zidebaktam (Zaynich®)

- Zidebaktam; hem **beta-laktamaz inhibitörüdür** hem de **PBP-2'ye bağlanarak** etki gösterir
- PBP2 ve PBP3'ün eş zamanlı inaktivasyonu, güçlü ve hızlı bir bakterisidal potansiyel kazandırır.
- **XDR Enterobacterales, *P. aeruginosa, A. baumannii ve S. maltophilia* ✓**
- Sınıf A, **B,** C ve **D** beta-laktamazlara karşı etkili
- Faz 3 çalışması (ID: NCT04979806) tamamlandı (06/2024)

Antimicrobial Agents and Chemotherapy

CHALLENGING CLINICAL CASE
August 2023 Volume 67 Issue 8 e00500-23
https://doi.org/10.1128/aac.00500-23

Successful Use of Cefepime-Zidebactam (WCK 5222) as a Salvage Therapy for the Treatment of Disseminated Extensively Drug-Resistant New Delhi Metallo-β-Lactamase-Producing *Pseudomonas aeruginosa* Infection in an Adult Patient with Acute T-Cell Leukemia

Praveen Kumar Tirlangi [a], Bala Saheb Wanve [b], Ramakanth Reddy Dubbudu [c], Boorgula Sushma Yadav [d], L. Siva Kumar [e], Anand Gupta [e], Racha Amarthya Sree [f], Hari Priya Reddy Challa [g], P. Naveen Reddy [h]

> Eur J Clin Microbiol Infect Dis. 2025 Mar 18. doi: 10.1007/s10096-025-05106-8.
Online ahead of print.

Investigational antibiotic cefepime/zidebactam as a therapeutic option for the treatment of an unyielding empyema in a paediatric patient caused by extensively drug-resistant Pseudomonas aeruginosa: a case report

Vishnu Rao Polati [1], Santosh Gattu [2], Venkata Nagarjuna Maturu [3], P Swati Prakasham [4], Maryam Maqsood [2 5]

> Eur J Clin Microbiol Infect Dis. 2024 Feb 28. doi: 10.1007/s10096-024-04791-1.
Online ahead of print.

Successful treatment of sino-pulmonary infection & skull base osteomyelitis caused by New Delhi metallo-β-lactamase-producing Pseudomonas aeruginosa in a renal transplant recipient by using an investigational antibiotic cefepime/zidebactam (WCK 5222)

Rajeev Soman [1 2], Rasika Sirsat [3], Ayesha Sunavala [4], Neha Punatar [5], Jugal Mehta [3], Camilla Rodrigues [6], Balaji Veeraraghavan [7]

Case Reports > Ann Clin Microbiol Antimicrob. 2023 Jul 5;22(1):55.
doi: 10.1186/s12941-023-00606-x.

Compassionate use of a novel β-lactam enhancer-based investigational antibiotic cefepime/zidebactam (WCK 5222) for the treatment of extensively-drug-resistant NDM-expressing Pseudomonas aeruginosa infection in an intra-abdominal infection-induced sepsis patient: a case report

Dilip Dubey [1], Manish Roy [2], Tajamul H Shah [3], Noor Bano [2], Vidushi Kulshrestha [2], Sandeep Mitra [2], Pushpender Sangwan [2], Madhulika Dubey [4], Ali Imran [2], Bhawna Jain [5], Aravind Velmurugan [6], Yamuna Devi Bakthavatchalam [6], Balaji Veeraraghavan [7]

* Dubey D, Roy M, Shah TH, et al. Compassionate use of a novel β-lactam enhancer-based investigational antibiotic cefepime/zidebactam (WCK 5222) for the treatment of extensively-drug-resistant NDM-expressing Pseudomonas aeruginosa infection in an intra-abdominal infection-induced sepsis patient: a case report. *Ann Clin Microbiol Antimicrob*. 2023;22(1):55. Published 2023 Jul 5.

* Polati VR, Gattu S, Maturu VN, Prakasham PS, Maqsood M. Investigational antibiotic cefepime/zidebactam as a therapeutic option for the treatment of an unyielding empyema in a paediatric patient caused by extensively drug-resistant Pseudomonas aeruginosa: a case report. *Eur J Clin Microbiol Infect Dis*. Published online March 18, 2025. doi:10.1007/s10096-025-05106-8

Table 6 In vitro activity of cefepime/zidebactam against MDR Gram-negative clinical isolates collections including metallo-β-lactamase producers

References	Country	Period of isolates collection	Breakpoint	Carbapenem non-susceptible and/or carbapenemase-producers			MβL producers			NDM producers
				Enterobacterales	*P. aeruginosa*	ACB	Enterobacterales	*P. aeruginosa*	ACB	Enterobacterales
[63]	Swiss	2022–23	EUCAST/CLSI	-	21/39; 53.8%	-	-	21/39; 53.8%	-	-
			Provisional BP	-	28/39; 71.8%	-	-	28/39; 71.8%	-	-
[128]	Spain	2018	EUCAST	398/400; 99.5%	-	-	52/56; 92.8%	-	-	10/10; 100%
			CLSI	384/400; 99.5%	-	-	46/56; 82.1%	-	-	10/10; 100%
			Provisional BP	400/400; 100%	-	-	54/56; 96.4%	-	-	10/10; 100%
[130]	India	2019–2021	EUCAST	553/569; 97.2%	-	-	402/418; 96.2%	-	-	-
			CLSI	529/569; 93%	-		379/418; 90.7%	-	-	-
			Provisional BP	569/569; 100%	-		418/418; 100%	-	-	-
[150]	Worldwide	-	EUCAST	984/1018; 96.7%	157/262; 59.9%	-	-	-	-	-
			CLSI	896/1018; 88%	157/262; 59.9%	-	-	-	-	-
			Provisional BP/PKPD	1003/1018; 98.5%	261/262; 99.6%	-	203/214; 94.8%	94/94; 100%	-	-
[151]	Taiwan	2012–2018	EUCAST	-	74/81; 91.3%	-	-	3/4; 75%	-	-
			CLSI	-	74/81; 91.3%	11/135; 8.1%	-	3/4; 75%	-	-
			Provisional BP	179/180; 99.4%	-	-	92/92; 100%	-	-	-
[152]	UK	2015–2016	EUCAST	568/619; 91.8%	91/96; 94.8%	-	183/234; 78.2%	76/81; 93.8%	-	-
			CLSI	536/619; 86.6%	91/96; 94.8%	98/202; 48.5%	155/234; 66.2%	76/81; 93.8%	0/19; 0%	-
			Provisional BP/PKPD	586/619; 86.6%	96/96; 100%	188/202; 93.1%	201/234; 85.6%	81/81; 100%	6/19; 31.6%	-
[153]	Greek	2014–2018	EUCAST	406/422; 96.2%	154/172; 89.5%	-	176/186; 94.6%	93/106; 87.7%	-	-
			CLSI	391/422; 92.6%	154/172; 89.5%	20/181; 11%	166/186; 89.2%	93/106; 87.7%	-	-
			Provisional BP	415/422; 98.3%	171/172; 99.4%	174/181; 96.1%	182/186; 97.8%	105/106; 99%	-	-
[154]	China	2019	Provisional BP	364/379; 96%	224/228; 98.2%	455/471; 96.6%	114/126; 90.5%	-	-	105/117; 89.7%
[155]	Worldwide	2018–2019	EUCAST	656/681; 96.3%	1108/1147; 96.6%	-	-	-	-	-
			CLSI	626/681; 91.9%	1108/1147; 96.6%	-	-	-	-	-
			Provisional BP	666/681; 97.8%	1146/1147; 99.9%	-	-	-	-	-
[156]	USA	-	EUCAST/CLSI	-	98/108; 90.7%	-	-	15/18; 83.3%	-	-
			Provisional BP	-	108/108; 100%	-	-	18/18; 100%	-	-
Pooled data		2012–2023	EUCAST	3565/3709; 96.1%	1703/1905; 89.4%	-	813/894; 90.9%	208/248; 83.9%	-	10/10; 100%
			CLSI	3362/3709; 90.6%	1703/1905; 89.4%	129/518; 24.9%	746/894; 83.4%	208/248; 83.9%	0/19; 0%	10/10; 100%
			Provisional BP	4182/4268; 98%	2034/2052; 99.1%	817/854; 95.7%	1264/1326; 95.3%	326/338; 96.4%	6/19; 31.6%	115/127; 90.5%

* Boattini M, Gaibani P, Comini S, et al. In vitro activity and resistance mechanisms of novel antimicrobial agents against metallo-β-lactamase producers. *Eur J Clin Microbiol Infect Dis*. Published online March 10, 2025. doi:10.1007/s10096-025-05080-1

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE
January/February 2022 Volume 10 Issue 1 e02678-21
https://doi.org/10.1128/spectrum.02678-21

Molecular Characterization of WCK 5222 (Cefepime/Zidebactam)-Resistant Mutants Developed from a Carbapenem-Resistant *Pseudomonas aeruginosa* Clinical Isolate

Xiaolei Pan[a], Xinrui Zhao[a], Yuqin Song[b], Huan Ren[a], Zhenyang Tian[c], Qi'an Liang[a], Yongxin Jin[a], Fang Bai[a], Zhihui Cheng[a], Jie Feng[b], Weihui Wu[a]

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[b]State Key Laboratory of Microbial Resources, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China

IMPORTANCE Antibiotic resistance imposes a severe threat on human health. WCK 5222 is a β-lactam/β-lactamase inhibitor combination that is composed of cefepime and zidebactam. It is one of the few antibiotics in clinical trials that are effective against multidrug-resistant *Pseudomonas aeruginosa*, including those producing metallo-β-lactamases. Understanding the mechanisms and development of bacterial resistance to WCK 5222 may provide clues for the development of strategies to suppress resistant evolvement. In this study, we performed an *in vitro* passaging assay by using a multidrug-resistant *P. aeruginosa* clinical isolate. Our results revealed that mutations in the zidebactam target protein PBP2 play a major role in the bacterial resistance to WCK 5222. We further demonstrated that the mutations reduced the affinities between PBP2 and zidebactam and resulted in functional resistance of PBP2 to zidebactam.

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkaf045

Journal of Antimicrobial Chemotherapy 50 years

Decreased susceptibility to cefepime/zidebactam among carbapenemase-producing *Escherichia coli* from Stockholm, Sweden with alterations in PBP2

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Results: Of the 150 isolates, 145 (96.6%) isolates had MICs <4 mg/L indicating susceptibility and 5 (3.3%) had MICs >4 mg/L. MICs for zidebactam alone among the five isolates with DS to cefepime/zidebactam were ≥8 mg/L. WGS analysis revealed that these five isolates were NDM-5 producers and belonged to ST405 ($n=1$), ST410 ($n=2$) and ST648 ($n=2$). Presence of four-amino-acid inserts (YRIK/YRIN) in PBP3 was observed in 80/150 (53.3%) isolates, and mutations leading to alterations in PBP2 were observed in 41/150 (27.3%) isolates. Presence of other β-lactamases (CTX-M group) and/or cephalosporinases (bla_{CMY}) did not have an impact on the susceptibility to cefepime/zidebactam. Three of the five isolates with DS had a V522I substitution in PBP2.

Conclusions: Our results indicate that DS to cefepime/zidebactam among clinical isolates of *E. coli* could arise due to targeted mutations in PBP2.

* Pan X, Zhao X, Song Y, et al. Molecular Characterization of WCK 5222 (Cefepime/Zidebactam)-Resistant Mutants Developed from a Carbapenem-Resistant Pseudomonas aeruginosa Clinical Isolate. *Microbiol Spectr*. 2022;10(1):e0267821. doi:10.1128/spectrum.02678-21

* Tellapragada C, Dunleavy C, Jonsson P, Giske CG. Decreased susceptibility to cefepime/zidebactam among carbapenemase-producing Escherichia coli from Stockholm, Sweden with alterations in PBP2. *J Antimicrob Chemother*. Published online February 17, 2025. doi:10.1093/jac/dkaf045

Reference	β-Lactams and β-lactam/ BLI combinations	CRE				CRAB OXA	CRPA
		A ESBL (CTX-M)	A KPC (KPC-2, -3)	D OXA (OXA-48)	B MBL (NDM)		
Approved	Vaborbactam + meropenem	•	•	•	X	X	X
Approved	Relebactam + imipenem + cilastatin	•	•	•	X	X	?
Approved	Cefiderocol	•	•	•	•	•	•
Approved	Sulbactam+ durlobactam (ETX-2514)	X	X	X	X	•	X
FDA onaylı	Cefepime + enmetazobactam (AAI-101)	•	?	X	X	X	X
FDA onaylı	Sulopenem	•	X	X	X	X	X
NCT03840148	Cefepime+ taniborbactam (VNRX-5133)	•	•	•	✓	x	✓
NCT04505683	Benapenem	X	X	X	X	X	X
NCT04979806	Cefepime + zidebactam	•	•	•	✓	✓	✓
NCT03491748	Cefpodoxime proxetil + ETX0282	•	•	•	X	X	X
NCT02972255	Meropenem + nacubactam (OP0595)	•	•	•	✓	X	?
NCT05072444	Xeruborbactam (QPX7728) + b-lactam (S-649228)	•	•	•	•	•	•
NCT05204368	Funobactam (XNW4107) + imipenem + cilastatin	•	•	?	X	?	X
NCT05488678	Ceftibuten + ledaborbactam (VNRX-7145)	•	•	•[d]	X	X	X
NCT05645757	Ertapenem + zidebactam	•	•	•[e]	X	X	?
NCT05887908	Cefepime + nacubactam (OP0595)	•	•	X	?[b]	X	?
NCT05887908	Aztreonam + nacubactam (OP0595)	•	•	•	•	X	X
NCT05905913	Meropenem + ANT3310	•	•	•	/	•	X
NCT05226923	Meropenem + KSP-1007 (MEROPEN)	?	?	?	?	?	?

➢ DİĞER ANTİBİYOTİKLER

Zoliflodasin

- Bakteriyel tip II topoizomerazları (GyrB) inhibe eden yeni bir antibiyotik sınıfı.
- Florokinolonlardan (GyrA) farklı bir bağlanma bölgelerine sahiptir !
- **XDR *N.gonorrhea*** ✓
- ESCMID Global 2024'de faz 3 çalışması;

  → 930 non-komplike *N.gonorrhea, MB yanıt* (6±2. gün)

  → Zoliflodasin %90,9 vs. CRO + Azitromisin %96,2

Gepotidasin (Blujepa ®)

- Bakteriyel DNA girazının GyrA alt birimini ve bakteriyel topoizomeraz IV'ün parC alt birimini inhibe eden yeni bir antibiyotik sınıfı.
- **XDR *N.gonorrhea*** ✓
- EAGLE-2 ve EAGLE-3 faz 3 çalışmalarında

  → EAGLE-2 (n=1531); NF'ye eş değer (+ %4,3)

  → EAGLE-3 (n=1605); NF'ye üstün (+ %14,6)
- FDA onayı 2025 (Komplike olmayan İYE)

* https://innovivaspecialtytherapeutics.com/innoviva-specialty-therapeutics-positive-phase-3-oral-zoliflodacin-data-for-the-treatment-of-uncomplicated-gonorrhea-announced-at-escmid-global-2024/

* Wagenlehner F, Perry CR, Hooton TM, et al. Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials. *Lancet*. 2024;403(10428):741-755. doi:10.1016/S0140-

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- Tamamen sentetik olan ilk florosiklin türevidir (Kimyasal yapısı ve etki spektrumu **tigesikline** benzer)
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- **CRE, CRAB, MRSA, VRE, Anerob ve tüberküloz dışı mikobakterilere ✓**
- ***P. aeruginosa*** → ETKİSİZ ! ***S. maltophilia*** → ??
- Oral biyoyararlanımı %28
- FDA ve EMA onayı (iv form) 2018 (KİAİ)

* Wright H, Bonomo RA, Paterson DL. New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn?. *Clin Microbiol Infect.* 2017;23(10):704-712. doi:10.1016/j.cmi.2017.09.001

Clinical Trial > JAMA Surg. 2017 Mar 1;152(3):224-232. doi: 10.1001/jamasurg.2016.4237.

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

Joseph Solomkin [1], David Evans [2], Algirdas Slepavicius [3], Patrick Lee [4], Andrew Marsh [5], Larry Tsai [5], Joyce A Sutcliffe [5], Patrick Horn [5]

→ Çok merkezli, RKÇ, Faz 3 (IGNITE-1) →KİAİ

→ Eravasiklin (n=270) vs. Ertapenem (n=271)

→ Klinik yanıt (25-31. gün) → Eravasiklin **%86,8**

→ Ertapenem **%87,6**

→ İlaca bağlı ciddi yan etki **%5,6** vs. **%6,0**

* Solomkin J, Evans D, Slepavicius A, et al. 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. *JAMA Surg*.

Clinical Trial > Clin Infect Dis. 2019 Aug 30;69(6):921-929. doi: 10.1093/cid/ciy1029.

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

Joseph S Solomkin [1], Janis Gardovskis [2], Kenneth Lawrence [3], Philippe Montravers [4 5 6], Angie Sway [7], David Evans [8], Larry Tsai [3]

→ Çok merkezli, RKÇ, Faz 3 (IGNITE-4) →KİAİ

→ Eravasiklin (n=250) vs. Meropenem (n=249)

→ Klinik yanıt (25-31. gün) → Eravasiklin **%90,8**

→ Meropenem **%91,2**

→ Yan etki nedenli tedavi kesimi **%1,6** vs. **%2,0**

* Solomkin JS, Gardovskis J, Lawrence K, et al. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections. *Clin Infect Dis*. 2019;69(6):921-

BV 100 (Rifabutin iv)

- Yarı-sentetik rifampisin, oral formu1992 yılında *Mycobacterium avium complex* için onay almıştır
- Siderofor reseptörü FhuE tarafından Gram-negatif bakteri türlerine seçici olarak girebilmekte
- ***XDR A. baumannii ✓***
- **Sefiderokol'e dirençli suşlar dahil olmak** üzere dirençli alt popülasyonlara etkin !
- Faz 2 çalışması Aralık 2024'de tamamlandı (CRAB ilşkili VAP, Kolistin + Rifabutin vs. En iyi alternatif)
- İn-vitro çalışmalarda **sefiderokolün aksine**, **maruziyet sonrası rifabutin direncinin** ortaya çıkması **nadir. (*Kolistin ile kombinasyon!!)**

* Arshad N, Azzam W, Zilberberg MD, Shorr AF. *Acinetobacter baumannii* Complex Infections: New Treatment Options in the Antibiotic Pipeline. *Microorganisms*. 2025;13(2):356. Published 2025 Feb 7. doi:10.3390/microorganisms13020356

Karbapenem Dirençli *A. Baumannii Complex* Tedavisindeki Yeni Antimikrobiyaller

Agent	Manufacturer/Sponsor	Clinical Status	Mechanism of Action	Targets Only ABC (Yes/No)	May Be Adjunct in Susceptible ABC Infections (Yes/No)
Cefiderocol	Shionogi	Approved	Siderophore cephalosporin	No	No
Sulbactam-Durlobactam	Innoviva Specialty Therapeutics	Approved *	Combination agent with BLI with enhanced anti-ABC activity	Yes	No
BV-100 (IV rifabutin)	Bioversys	Phase II	Rifamycin	Yes	No
Cefepime-zidebactam	Wockhardt	Phase III	Novel BLI with anti-ABC activity	No	No
Zosurabalpin	Roche	Phase II/III	Novel macrocyclic peptide	Yes	No
OMN6	Omnix Medical	Phase II	Antimicrobial peptide	Yes	Yes

Abbreviations: ABC—*A. baumannii* complex, BLI—beta-lactamase inhibitor, IV—intravenous. * Only in the United States.

* Arshad N, Azzam W, Zilberberg MD, Shorr AF. *Acinetobacter baumannii* Complex Infections: New Treatment Options in the Antibiotic Pipeline. *Microorganisms*. 2025;13(2):356. Published 2025 Feb 7. doi:10.3390/microorganisms13020356

ÖZET

- XDR *N.gonorrhea* → Zoliflodasin, **Gepotidasin** (Blujepa®)
- ESBL+ bakteri infeksiyonlarında karbapenemleri korumak için→ **Sefepim/Enmetazobaktam** (Exblifep®)
- ESBL+ bakteri infeksiyonlarında hastane yatış süresini kısaltmak için → **Sulopenem/Probenesid** (Orlynvah®), Tebipenem Hbr
- **Sefiderokol** (Fetroja® / Fectroja®) → XDR GNB, **Heterodirenç !!,** tedavi sırasında direnç !!, ***A.baumanii*** *
- **Aztreonam-Avibaktam** (Emblaveo ®) → XDR Enterobacterales, **MBL + *P. aeruginosa*** zayıf etkili !!
- Sefepim / Taniborbaktam → XDR Enterobacterales, **Heterodirenç !!,** Bazı **grup B** beta-laktamazlara etkisiz !
- **Sefepim / Zidebaktam** (Zaynich ®) ★ → XDR GNB, in-vitro duyarlılık sonuçları ⬆
- **Taniborbaktam, Xeruborbaktam , Zidebaktam, Nakubaktam** kombinasyonları !!

TEŞEKKÜRLER..