Yeni Tedavi Seçenekleri Ceftazidime-Avibactam

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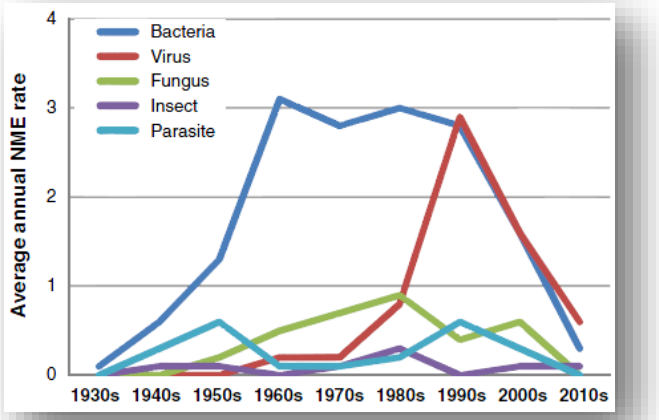
The antibiotic era

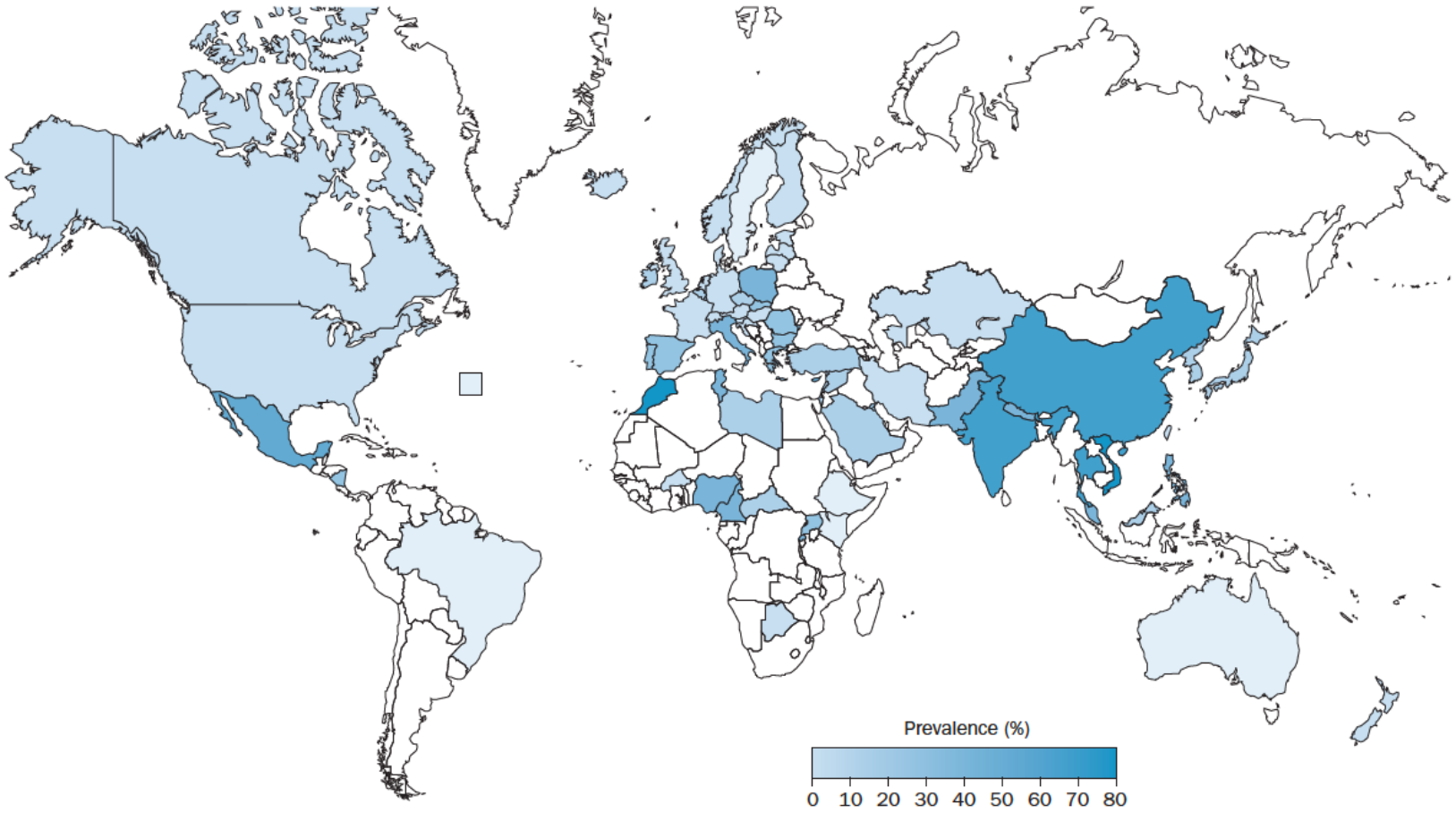
1950-60s	1970-90s	2000s	2010s
Small spectrum	Broad spectrum	Small spectrum	Small spectrum
Gram positive	Gram negative Gram positive	Gram positive	Gram negative targeted
Natural products	Medicinal chemistry, Semisynthetic products	Target based	Natural products? Alternative approaches?

Golden years of pills and profits

Fixing selected resistance problems



MS Kinch et al: Drug Discovery Today 2014, 19 (9)

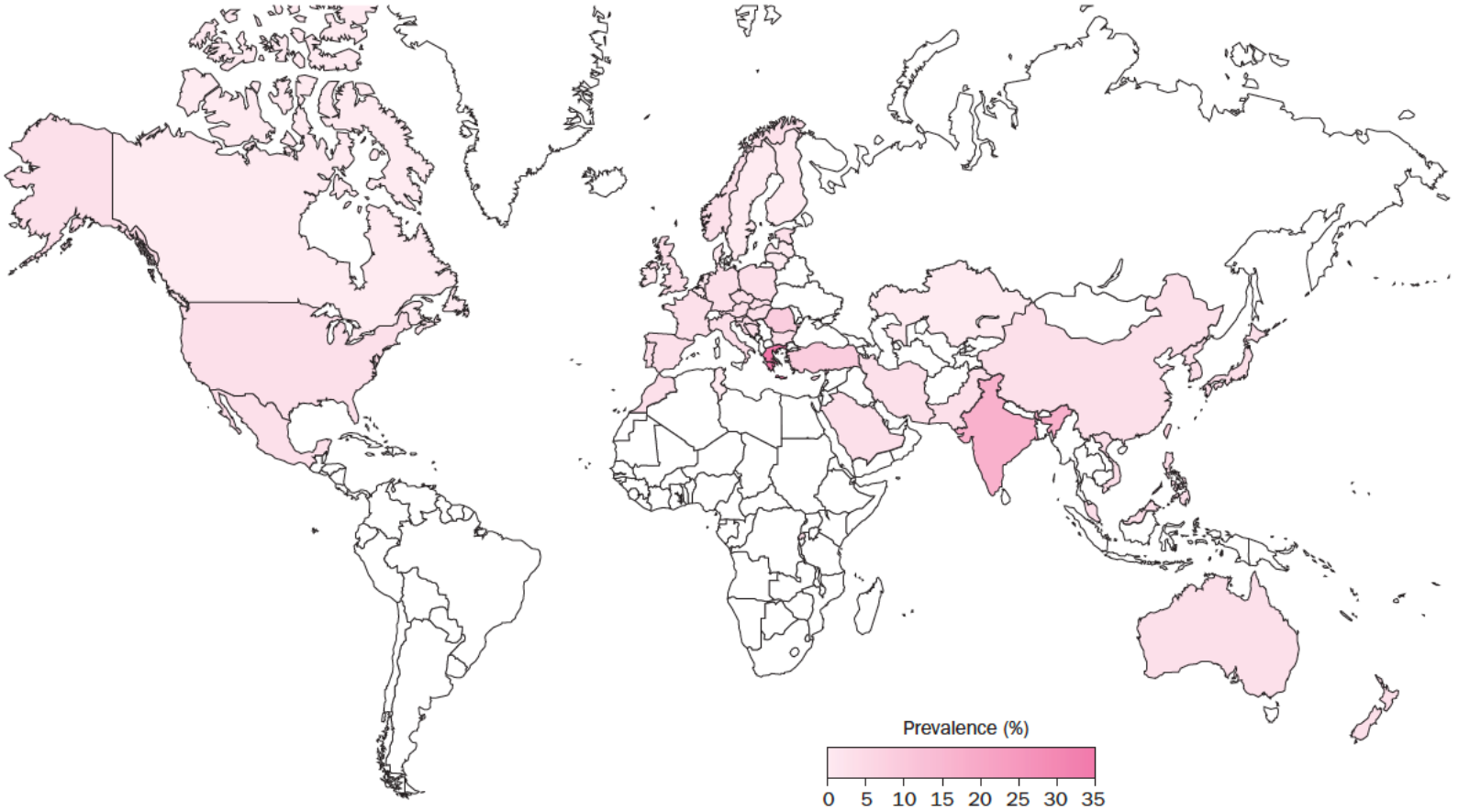


Gram-negatif üropatojenlerde kinolon direnci

Nature Reviews Urology **(12)**, p 570–584 (2015)

Gram-negatif üropatojenlerde 3. kuşak sefalosporin direnci

Nature Reviews Urology **(12)**, p 570–584 (2015)



Gram-negatif üropatojenlerde karbapenem direnci

Nature Reviews Urology **(12)**, p 570–584 (2015)

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Delafloxacin[a]	NDA[1]	Fluoroquinolone	IV & oral (Melinta)	■	■	■	□	✖	✖	✖	✖
Vaborbactam + meropenem (Carbavance)	NDA	Boronate BLI + carbapenem	IV (The Medicines Co)	■	■	□	[b]	✓	✖	✖	▰

Vaborbactam: Class A β-laktamazlara etkili, MBL ve OXA etkinliği zayıf

Relebactam: Class A ve C β-laktamazları inhibe eder

C, yeni kimyasal sınıf MoA, yeni etki mekanizması T, yeni hedef NCR, çapraz direnç yok

□ active, ▰ possibly active, ■ not or insufficiently active.

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Cefiderocol	3	Siderophore-cephalosporin	IV (Shionogi)	■	■	■		✖	✖	✖	✎
Relebactam + imipenem/ cilastatin	3	DBO-BLI + carbapenem/ degradation inhibitor	IV (Merck & Co)	■	■	■	[b]	✖	✖	✖	✖

Relebactam: Class A ve C β-laktamazları inhibe eder, diğerlerine etki zayıf

■ active, ■ possibly active, ■ not or insufficiently active.

Name (synonym)	Phase	Antibiotic class	Route of Administration (Developer)	Expected activity against priority pathogens				Innovativeness			
				CRAB	CRPA	CRE	OPP	C	T	MoA	NCR
Sulopenem	3	Carbapenem	IV & oral (Iterum)	■	■	■	■[c]	✖	✖	✖	✖
Plazomicin	3	Aminoglycoside	IV (Achaogen)	■	■	▒		✖	✖	✖	✖
Lascufloxacin	3	Fluoroquinolone	IV & oral (Kyorin)	■	■	■	▒	✖	✖	✖	✖
Eravacycline	3	Tetracycline	IV & oral (Tetraphase)	▒	■	▒		✖	✖	✖	✖
Omadacycline	3	Tetracycline	IV & oral (Paratek)	■	■	■	▒	✖	✖	✖	✖
Solithromycin	3	Macrolide	IV & oral (Cempra)	■	■	■	▒	✖	✖	✖	✖
Iclaprim	3	DHFR-inhibitor	IV (Motif Bio)	■	■	■	▒	✖	✖	✖	✖
Lefamulin	3	Pleuromutilin[4]	IV & oral (Nabriva)	■	■	■	▒	✔[d]	✖	✔	▒

Plazomicin: NDM üretenlerde sık bulunan 16S rRNA methylases ilacı parçalar

Omadacycline: eravacycline ve tigecycline kıyasla daha iyi farmakokinetiği var, linear; plasma protein bağlanma: 20–30%

Iclaprim: Yeni Dihydrofolate reductase inhibitörü, non-inferiority çalışmaları başarısız

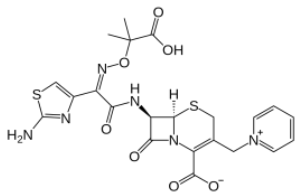
▒ active, ▒ possibly active, ■ not or insufficiently active.

Ülkemizde yakın gelecekte…

Drug	Phase I*	Phase II*	Phase III*	FDA approved
β-lactam combined with β-lactamase inhibitors				
Ceftazidime–avibactam[138]	✓	✓	✓	✓
Ceftolozane–tazobactam[139]	✓	✓	✓	✓
Ceftaroline fosamil–avibactam	✓	✓	–	–

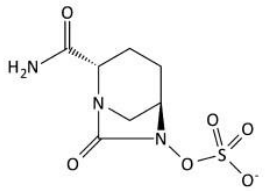
Caz-Avi, dirençli Gram (-) enfeksiyonların tedavisi için geliştirilmiş “Seftazidim” ve “Avibaktam” içeren ve karbapenemazlara karşı etkili olan ilk kombinasyondur[2,3,4].

“Seftazidim” ve “Avibaktam” içeren yeni bir kombinasyondur[2,3]



Seftazidim,

antipseudomonal, genişletilmiş spektrumlu bir 3. kuşak sefalosporindir



Avibaktam,

yeni geliştirilen bir non-β-laktam, β-laktamaz inhibitorüdür4.

FDA tarafından Şubat 2015’te, EMA tarafından Haziran 2016’da aşağıdaki endikasyonlarda onaylanmıştır

Komplike intra-abdominal enfeksiyonlar **(cIAI)**

Komplike üriner sistem enfeksiyonları **(cUTI)**

Hastanede kaynaklı pnömoni **(HAP)**

Erişkinlerde sınırlı tedavi seçeneği olan aerobik Gram (-) enfeksiyonların tedavisi (Yalnızca EMA)

1. Approval in other markets may include all of some of these four indications

Source: Bush K. A resurgence of β-lactamase inhibitor combinations effective against multidrug-resistant Gram-negative pathogens. Int J Antimicrob Agents 2015;46:483-493. Ceftazidime/Avibactam: Summary of product characteristics, 2016

Ülkemizde Ergönül Ö. ve arkadaşları tarafından yapılan en yakın tarihli ve çok merkezli çalışmada (2016) direnç oranları aşağıdaki gibidir:

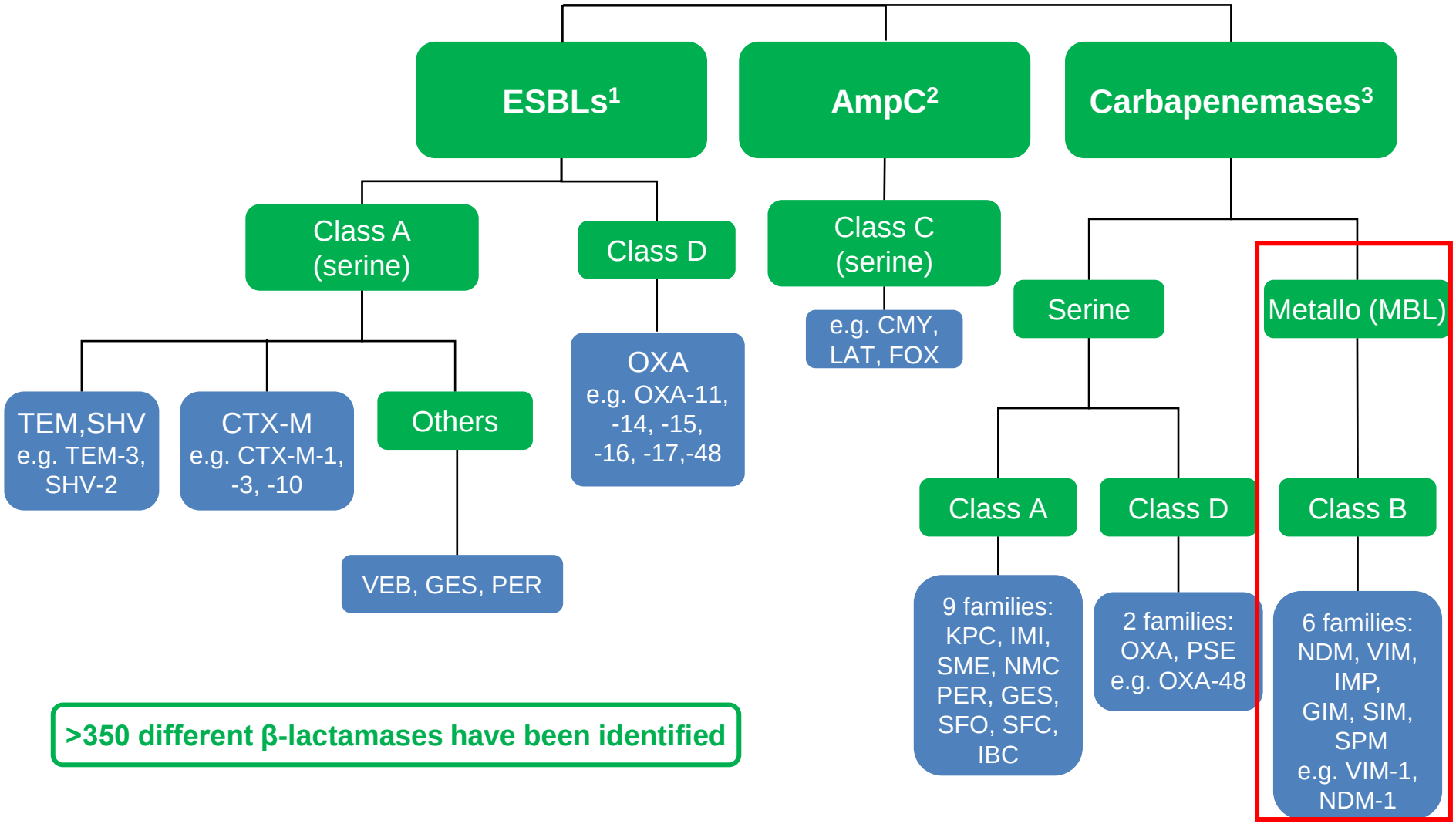
	E.coli		K.pneumoniae	
	3. Kuşak Sefalosporinlere Direnç Oranları	Karbapenemlere Direnç Oranları	3. Kuşak Sefalosporinlere Direnç Oranları	Karbapenemlere Direnç Oranları
Ergönül Ö. ve arkadaşları	71%	%6,4	72%	40%

7 farklı coğrafi bölge ve 17 üçüncü basamak sağlık merkezi çalışmaya dahil edilmiştir

Karbapenemler, çoklu ilaç dirençli (MDR) bakteriyel enfeksiyonların tedavisinde tercih edilen son çare ilaçlardır ve karbapenem dirençli Enterobacteriaceae'nin (CRE) yaygınlaşmış olması nedeniyle tehdit altındadır[5,10,11]. Karbapenem direncinin yayılması küresel bir sağlık krizidir[5,10,11].

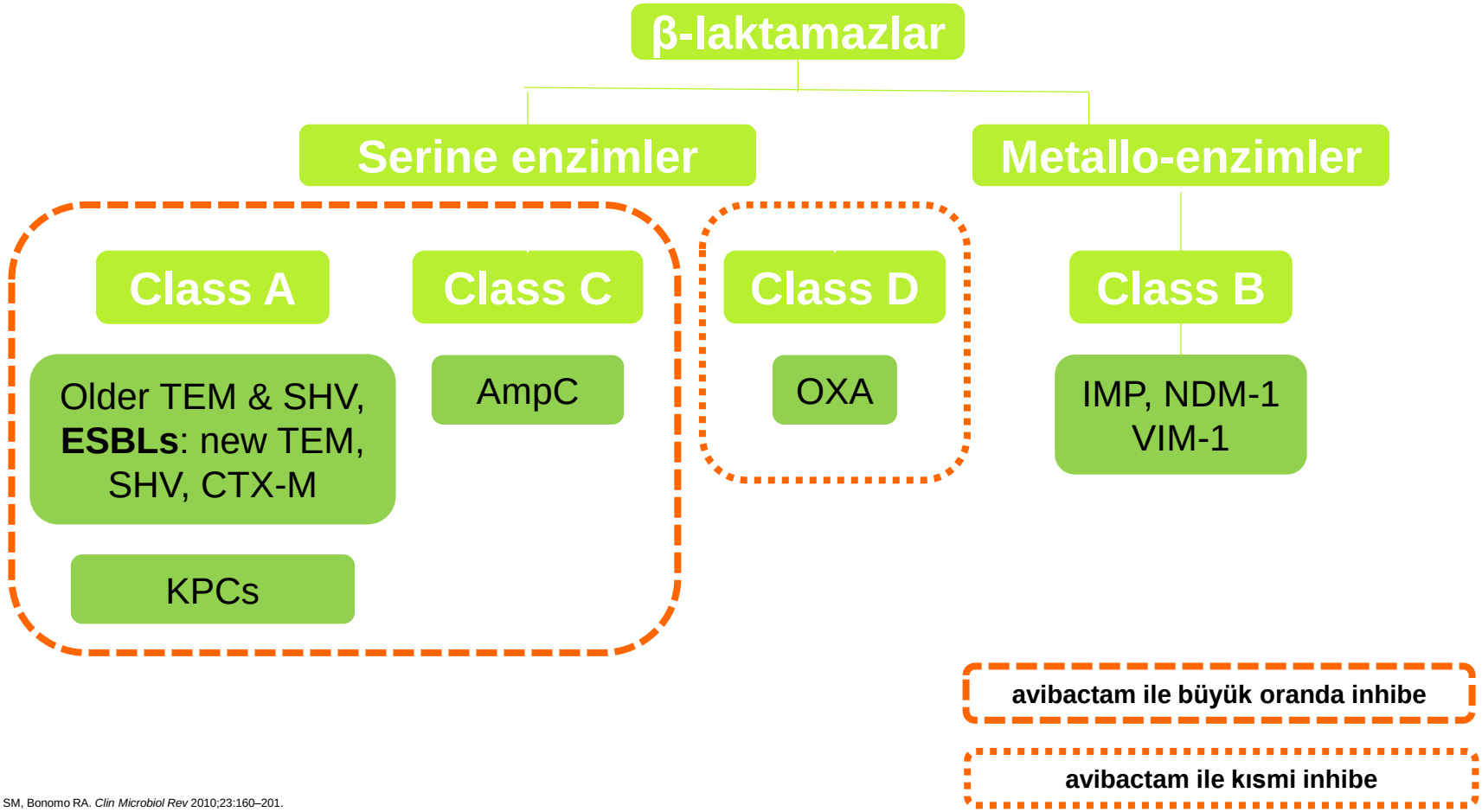
Ref : Ergönül Ö et al. Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality. Journal of Hospital Infection 94 (2016) 381-385

β-laktamaz ailesi



>350 different β-lactamases have been identified

Ceftazidime/Avibactam etkinliği



Drawz SM, Bonomo RA. *Clin Microbiol Rev* 2010;23:160–201.

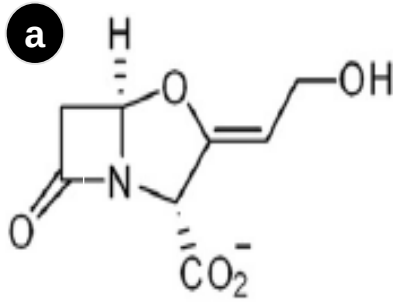
β-laktamazlar, protein sıralamalarına göre sınıf A-D arasında sınıflandırılan büyük bir hidrolitik enzim grubudur[16].

Şu ana kadar klinik kullanım için onaylanmış olan üç adet β-laktam β-laktamaz inhibitörü mevcuttur;

Klavulanik asid (klavulanat), sulbaktam and tazobaktam[16].

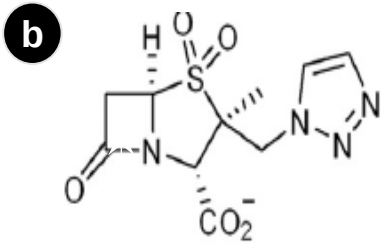
- Özellikleri şunlardır[16];
  - Yapısal olarak β-laktamlarla ilişkilidirler
  - Düşük düzeyde enzim ekspresyonu ile hidrolize olurlar
  - Sınıf C ve D enzimlerine karşı etkisizdirler

Klavulanik asid (klavulanat),



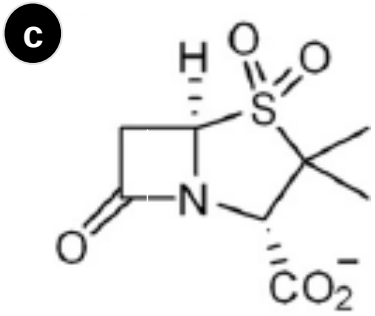
β-lactam ring

Tazobaktam



β-lactam ring

Sulbaktam



β-lactam ring

Lahiri SD, et al. Antimicrob Agents Chemother 2013;57:2496–505; Coleman 2011

Diazabicyclooctanes (DBOs; eg. Avibactam)

Beta laktamazlarda inhibisyon sırasında beta laktam halkaları açılır ancak Avibactam da bu gerçekleşmez ve stabilite korunur.

Çok potent bir inhibisyon yapar;

- 1 molekül beta laktamazı bloke etmek için 55-214 tazobactam ve klavulanik asid gerekirken, sadece 1-5 Avibactam yeterlidir.
- Enzim inhibitör kompleksinin yarılanma ömrü Tazobactamda 5 saat iken, Avibaktamda 7 günden uzundur.
- Sınıf C Beta laktamazların çoğu Klavulanik asid ile indüklenir ve eşkil ettiği antibiyotiğin MIC değerini yükseltirken, Avibactam indükleme yapmaz.

Coleman 2011

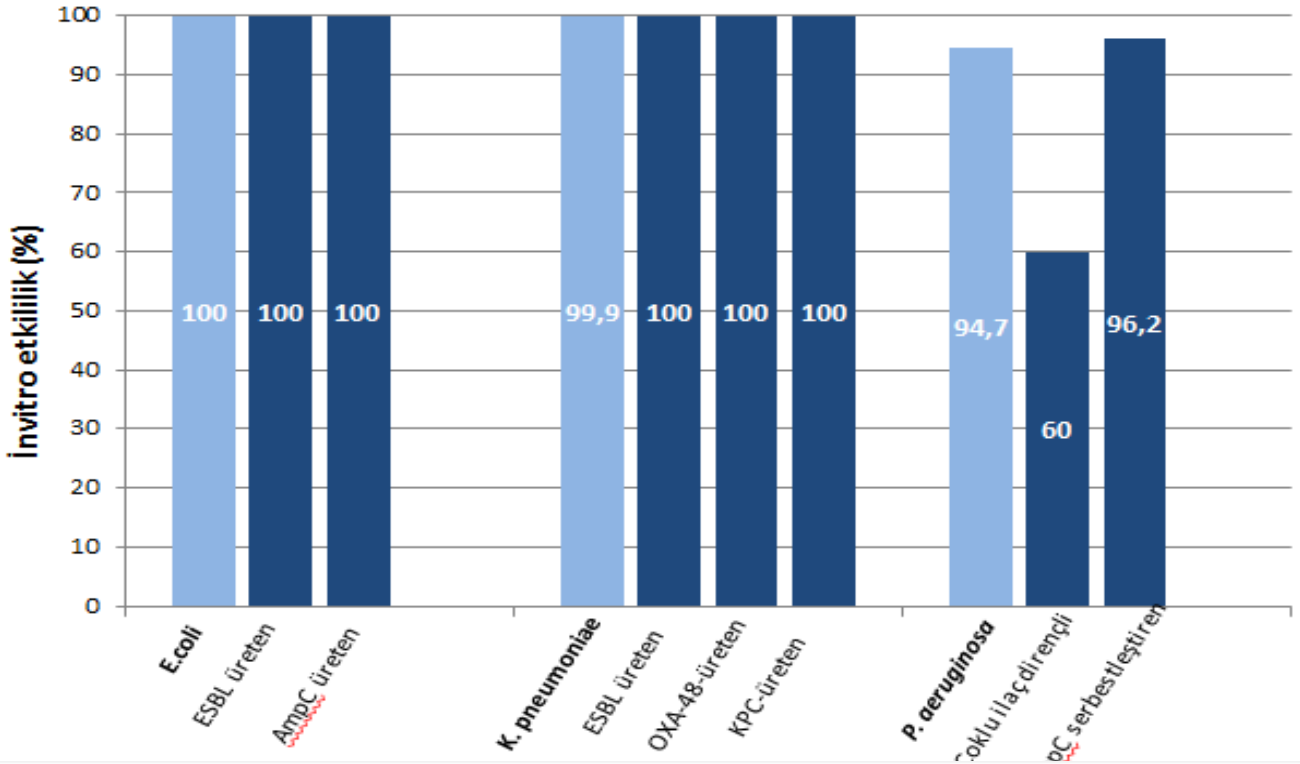
Avibaktam daha geniş β-laktamaz spektrumuna sahiptir:

		Klavulanik asid (klavulanat)	Tazobaktam	Avibaktam
Sınıf A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Sınıf B	IMP, VIM, NDM1	✗	✗	✗
Sınıf C	Chromosomal Enterobacteriaceae AmpC	✗	✗	✓
	Chromosomal Pseudomonas AmpC	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Sınıf D	OXA-1, -31, -10, -13	Variable **OXA-1, -10**	Variable	Variable **OXA-1, -31**
	Carbapenemase-type OXA-23, -40, -48, -58	Variable	Variable **OXA-23, -48**	Variable **OXA-48**

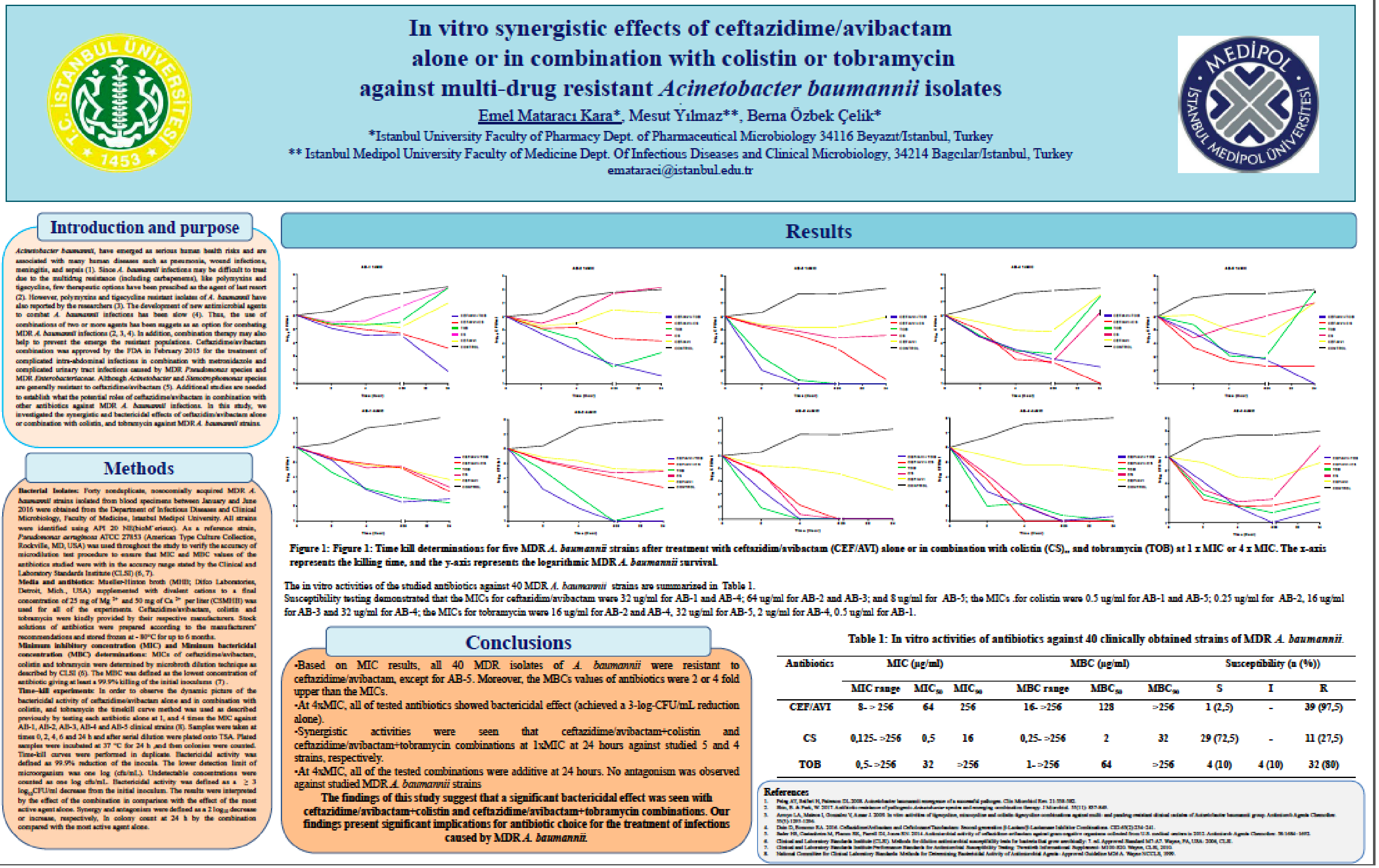
1. Lagacé-Wiens P, et al. *Core Evid* 2014;9:13–25.

Seftazidim Avibaktam etkililiği "invitro olarak" gösterilmiştir

CAZ-AVI genişletilmiş spektrumlu β-laktamaz (GSBL)-üreten bakteriler, Klebsiella pneumonia karbapenemaz (KPC)-üreten bakteriler, ve tedavisi zor Pseudomonas aeruginosa da dahil olmak üzere karbapeneme-dirençli Enterobacteriaceae (CRE)'ler gibi yaygın bir kapsamda etkisi "invitro olarak" gösterilmiştir



AstraZeneca Global Surveillance of 2015:
Ceftazidime-Avibactam Activity Tested Against Clinical Isolates in Europe



In vitro synergistic effects of ceftazidime/avibactam alone or in combination with colistin or tobramycin against multi-drug resistant *Acinetobacter baumannii* isolates

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Introduction and purpose

Acinetobacter baumannii, have emerged as serious human health risks and are associated with many human diseases such as pneumonia, wound infections, meningitis, and sepsis (1). Since *A. baumannii* infections may be difficult to treat due to the multidrug resistance (including carbapenems), like polymyxins and tigecycline, few therapeutic options have been prescribed as the agent of last resort (2). However, polymyxins and tigecycline resistant isolates of *A. baumannii* have also reported by the researchers (3). The development of new antimicrobial agents to combat *A. baumannii* infections has been slow (4). Thus, the use of combinations of two or more agents has been suggets as an option for combating MDR *A. baumannii* infections (2, 3, 4). In addition, combination therapy may also help to prevent the emerge the resistant populations. Ceftazidime/avibactam combination was approved by the FDA in February 2015 for the treatment of complicated intra-abdominal infections in combination with metronidazole and complicated urinary tract infections caused by MDR *Pseudomonas* species and MDR *Enterobacteriaceae*. Although *Acinetobacter* and *Stenotrophomonas* species are generally resistant to ceftazidime/avibactam (5). Additional studies are needed to establish what the potential roles of ceftazidime/avibactam in combination with other antibiotics against MDR *A. baumannii* infections. In this study, we investigated the synergistic and bactericidal effects of ceftazidim/avibactam alone or combination with colistin, and tobramycin against MDR *A. baumannii* strains.

Methods

Bacterial Isolates: Forty nonduplicate, nosocomially acquired MDR *A. baumannii* strains isolated from blood specimens between January and June 2016 were obtained from the Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Istanbul Medipol University. All strains were identified using API 20 NE(bioM´erieux). As a reference strain, *Pseudomonas aeruginosa* ATCC 27853 (American Type Culture Collection, Rockville, MD, USA) was used throughout the study to verify the accuracy of microdilution test procedure to ensure that MIC and MBC values of the antibiotics studied were with in the accuracy range stated by the Clinical and Laboratory Standards Institute (CLSI) (6, 7).

Media and antibiotics: Mueller-Hinton broth (MHB; Difco Laboratories, Detroit, Mich., USA) supplemented with divalent cations to a final concentration of 25 mg of Mg^{2+} and 50 mg of Ca^{2+} per liter (CSMHB) was used for all of the experiments. Ceftazidime/avibactam, colistin and tobramycin were kindly provided by their respective manufacturers. Stock solutions of antibiotics were prepared according to the manufacturers' recommendations and stored frozen at - 80°C for up to 6 months.

Minimum inhibitory concentration (MIC) and Minimum bactericidal concentration (MBC) determinations: MICs of ceftazidime/avibactam, colistin and tobramycin were determined by microbroth dilution technique as described by CLSI (6). The MBC was defined as the lowest concentration of antibiotic giving at least a 99.9% killing of the initial inoculums (7).

Time–kill experiments: In order to observe the dynamic picture of the bactericidal activity of ceftazidime/avibactam alone and in combination with colistin, and tobramycin the timekill curve method was used as described previously by testing each antibiotic alone at 1, and 4 times the MIC against AB-1, AB-2, AB-3, AB-4 and AB-5 clinical strains (8). Samples were taken at times 0, 2, 4, 6 and 24 h and after serial dilution were plated onto TSA. Plated samples were incubated at 37 °C for 24 h ,and then colonies were counted. Time-kill curves were performed in duplicate. Bactericidal activity was defined as 99.9% reduction of the inocula. The lower detection limit of microorganism was one log (cfu/mL). Undetectable concentrations were counted as one log cfu/mL. Bactericidal activity was defined as a ≥ 3 log_{10}CFU/ml decrease from the initial inoculum. The results were interpreted by the effect of the combination in comparison with the effect of the most active agent alone. Synergy and antagonism were defined as a 2 log_{10} decrease or increase, respectively, In colony count at 24 h by the combination compared with the most active agent alone.

Results

Figure 1: Figure 1: Time kill determinations for five MDR *A. baumannii* strains after treatment with ceftazidim/avibactam (CEF/AVI) alone or in combination with colistin (CS),, and tobramycin (TOB) at 1 x MIC or 4 x MIC. The x-axis represents the killing time, and the y-axis represents the logarithmic MDR *A. baumannii* survival.

The in vitro activities of the studied antibiotics against 40 MDR *A. baumannii* strains are summarized in Table 1.

Susceptibility testing demonstrated that the MICs for ceftazidim/avibactam were 32 ug/ml for AB-1 and AB-4; 64 ug/ml for AB-2 and AB-3; and 8 ug/ml for AB-5; the MICs .for colistin were 0.5 ug/ml for AB-1 and AB-5; 0.25 ug/ml for AB-2, 16 ug/ml for AB-3 and 32 ug/ml for AB-4; the MICs for tobramycin were 16 ug/ml for AB-2 and AB-4, 32 ug/ml for AB-5, 2 ug/ml for AB-4, 0.5 ug/ml for AB-1.

Table 1: In vitro activities of antibiotics against 40 clinically obtained strains of MDR *A. baumannii*.

Antibiotics	MIC (µg/ml)			MBC (µg/ml)			Susceptibility (n (%))		
	MIC range	MIC_{50}	MIC_{90}	MBC range	MBC_{50}	MBC_{90}	S	I	R
CEF/AVI	8- > 256	64	256	16- >256	128	>256	1 (2,5)	-	39 (97,5)
CS	0,125- >256	0,5	16	0,25- >256	2	32	29 (72,5)	-	11 (27,5)
TOB	0,5- >256	32	>256	1- >256	64	>256	4 (10)	4 (10)	32 (80)

Conclusions

- Based on MIC results, all 40 MDR isolates of *A. baumannii* were resistant to ceftazidime/avibactam, except for AB-5. Moreover, the MBCs values of antibiotics were 2 or 4 fold upper than the MICs.
- At 4xMIC, all of tested antibiotics showed bactericidal effect (achieved a 3-log-CFU/mL reduction alone).
- Synergistic activities were seen that ceftazidime/avibactam+colistin and ceftazidime/avibactam+tobramycin combinations at 1xMIC at 24 hours against studied 5 and 4 strains, respectively.
- At 4xMIC, all of the tested combinations were additive at 24 hours. No antagonism was observed against studied MDR *A. baumannii* strains

The findings of this study suggest that a significant bactericidal effect was seen with ceftazidime/avibactam+colistin and ceftazidime/avibactam+tobramycin combinations. Our findings present significant implications for antibiotic choice for the treatment of infections caused by MDR *A. baumannii*.

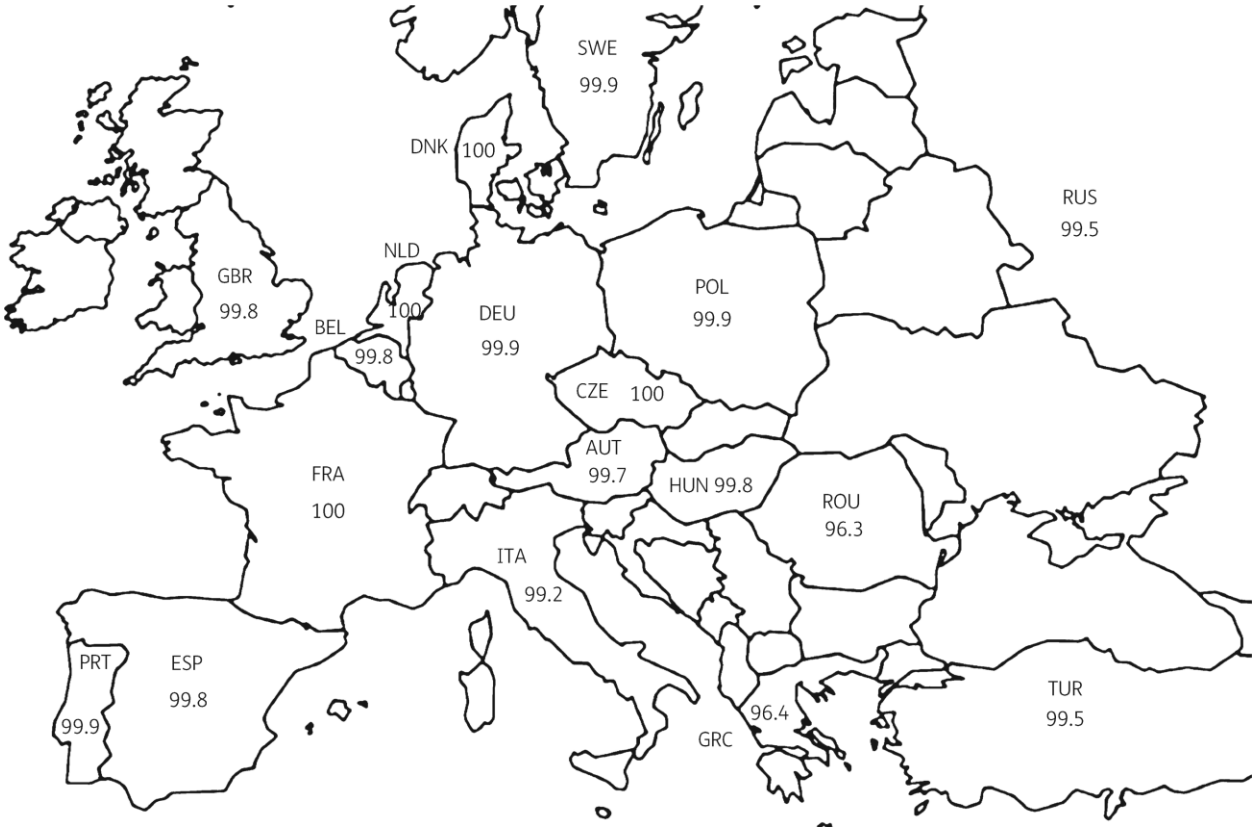
References

Acinetobacter baumannii CAZ-AVI dirençli kökenler kolistin ve tobramisin ile sinerjistik

- 18 Avrupa ülkesi 96 merkezden toplanan 24750 Enterobacteriaceae izolatı
- Caz/avi tüm karşılaştırmalarda en etkili ajan
- Tüm Enterobacteriaceae koleksiyonunda (%99.4 duyarlı)
- Kolistin-dirençli (%98.2% duyarlı),
- MDR (%96.7 duyarlı)
- CRE, MBL-negatif (98.5% duyarlı) isolates.
- Beklendiği üzere MBL taşıyan izolatlara etkisiz

From: In vitro activity of ceftazidime/avibactam against isolates of Enterobacteriaceae collected in European countries: INFORM global surveillance 2012–15

J Antimicrob Chemother. 2018;73(10):2782-2788. doi:10.1093/jac/dky266



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J Antimicrob Chemother. 2018;73(10):2782-2788. doi:10.1093/jac/dky266

Ceftazidime-avibactam clinical efficacy

Clinical trial programme overview

Seven prospective, international, multicentre, randomised Phase III studies

RECLAIM 1, 2 and 3: Adults with cIAI

Double-blind randomisation (1:1):

- CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg IV q8h *or*
- MER 1000 mg IV + placebo q8h

Primary objective:

- RECLAIM 1 and 2: Assess non-inferiority of CAZ-AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations)
- RECLAIM 3: Proportion of patients with clinical cure at TOC visit (CE populations)

RECAPTURE 1 and 2: Adults with cUTI (including acute pyelonephritis)

Double-blind randomisation (1:1) :

- CAZ 2000 mg + AVI 500 mg q8h IV *or*
- DOR 500 mg + placebo q8h IV

Primary objective:

Assess non-inferiority of CAZ-AVI on co-primary endpoints in mMITT analysis set:

1) Resolution of UTI-specific symptoms
2) Resolution/improvement of flank pain
3) Per-patient microbiol eradication and symptomatic resolution

REPRISE Adults with CAZ-resistant pathogens

Open-label randomisation (1:1) :

- CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg q8h IV *or*
- Best available therapy

Primary objective:

Estimate per-patient clinical response to CAZ-AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative pathogens

REPROVE Adults with nosocomial pneumonia (including VAP)

Double-blind randomisation (1:1) :

- CAZ 2000 mg + AVI 500 mg q8h IV *or*
- MER 1000 mg + placebo q8h IV

Plus open-label empiric linezolid + aminoglycoside

Primary objective:

Assess non-inferiority of CAZ-AVI on clinical cure rate at TOC visit in cMITT and CE populations

CE, clinically evaluable; cMMIT, clinically modified intent-to-treat; mMIITT, microbiological modified intent-to-treat

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia.

Shields RK[1,2], Nguyen MH[3,2], Chen L[4], Press EG[1], Potoski BA[1,2,5], Marini RV[2], Doi Y[1,2], Kreiswirth BN[4], Clancy CJ[1,6,7].

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- Ceftazidime-avibactam carbapenem-resistant *Klebsiella pneumoniae* bakteriyemisindealternatifler ile kıyaslandığında daha yüksek klinik başarı (P = 0.006) ve sağkalım (P = 0.01).

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Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *bla*$_{KPC-3}$ Mutations during Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections.

Shields RK[1,2], Chen L[3], Cheng S[1], Chavda KD[3], Press EG[1], Snyder A[1], Pandey R[3], Doi Y[1], Kreiswirth BN[3], Nguyen MH[4,2], Clancy CJ[1,2,5].

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- 3 hastanın tedavisi sırasında Ceftazidime-avibactam- dirençli *K. pneumoniae* gelişmiş- tedavinin 10 – 19. günlerinde
- Tüm genom dizileme ile daha önce bulunmayan *bla*$_{KPC-3}$ mutasyonları saptanmış

Antimicrob Agents Chemother. 2017 Feb 23;61(3)

Ceftazidime-avibactam PK/PD data

Anahtar noktalar

- Ceftazidime ve avibactam arasında ilaç-ilaç etkileşimi yok [1]
- Ceftazidime ve avibactam böbrekten atılır; idrarda ~%100 değişmeden atılır [2]
- Yaş ve cinsiyete göre doz ayarlaması yok [3]
- Ceftazidime-avibactam akciğer geçişi iyi; plazmaya yakın oranlarda geçer [4]
- Orta-ağır böbrek yetmezliğinde doz ayarlaması yapılır [2]
- Ceftazidime-avibactam 2000–500 mg q8h 2 saati aşan infüzyon ile uygulanır [5]
- Monte Carlo simulasyonuna göre bu dozda ciddi Gram-negatif enfeksiyonlar için hedefi tutturur (ceftazidime 50% *f*T>MIC; avibactam 50% *f*T>CT 1 mg/L)[6]

1. Edeki T et al. ICAAC 2013; Poster A-1019; 2. Merdjan H et al. *Clin Drug Investig.* 2015;35:307–317; 3. Tarral A, Merdjan H. *Clin Ther*. 2015;37(4):877–886; 4. Nicolau D et al. ICAAC 2013; Poster A-1027; 5. Crandon JL et al. *Antimicrob Agents Chemother*