Antimikrobiyal Mücadelede Yeni Bakış Yeni Başlangıç

Prof. Dr. Füsun CAN

Koç Üniversitesi Tıp Fakültesi Tıbbi Mikrobiyoloji AD

Koç Üniversitesi İş Bankası Enfeksiyon Hastalıkları Araştırma Merkezi (KUISCID)

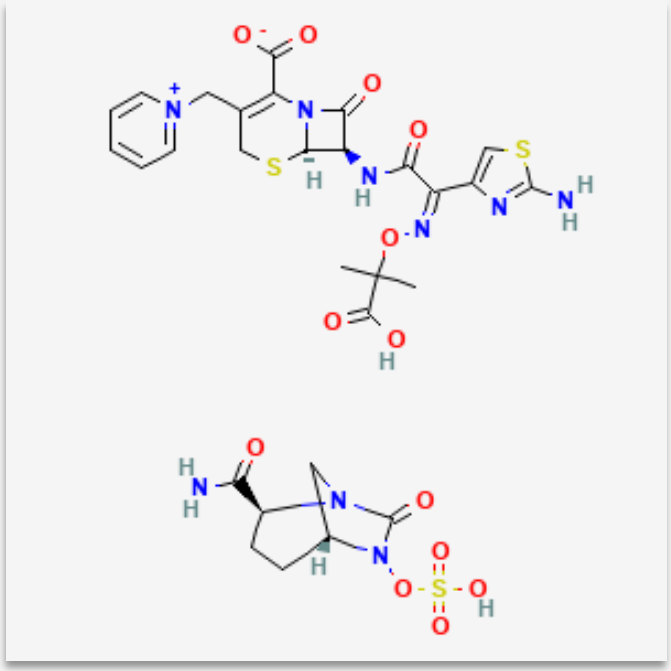
Sunum Planı

- Seftazidim Avibaktam kullanımın klinik yararlanımı
- Uluslararası ve ulusal seftazidim avibaktam direnç çalışmalarından örnekler
- Seftazidim avibaktam direncini saptamaya yönelik testler
- Direnç mekanizmaları
  - *K.pneumoniae*
  - *P.aeruginosa*

ESKAPE Patojenler ile Mücadele

Seftazidim-Avibaktam

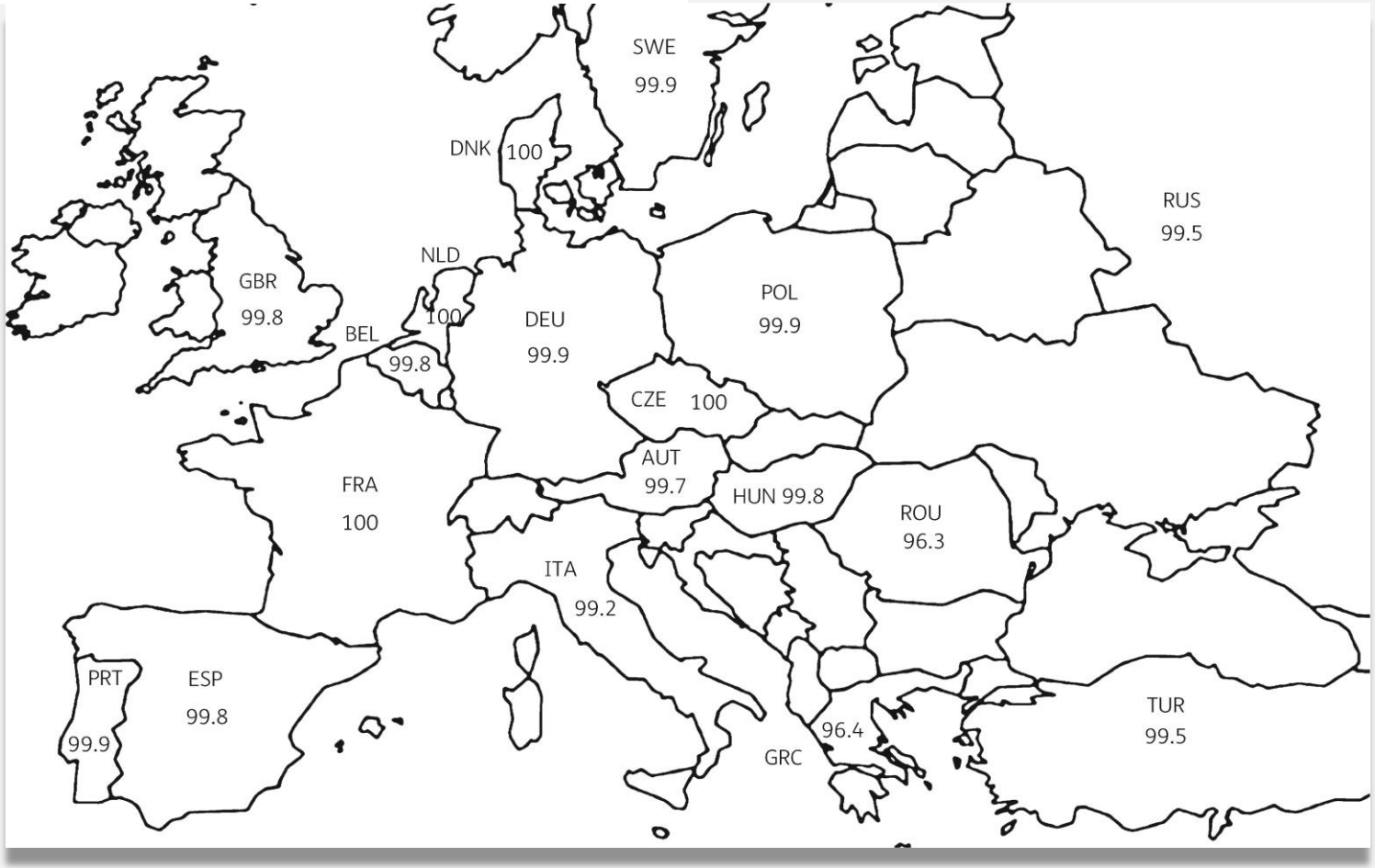
Etki spektrumu:
Karbapenem dirençli
Enterobacterales ve P.aeruginosa
Amber Class A(KPC), Class C, Class D (OXA-48)
metallobatalaktamazlara karşı etkisiz (NDM, VİM, İMP)



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

Krystyna M Kazmierczak, Boudewijn L M de Jonge, Gregory G Stone, Daniel F Sahm

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 10, October 2018, Pages 2782–2788, https://doi.org/10.1093/jac/dky266



Türkiye’de Ceftazidim-Avibactam Direnç Oranları

> Acta Microbiol Immunol Hung. 2021 Jul 29. doi: 10.1556/030.2021.01525. Online ahead of print.

Ceftazidime - Avibactam susceptibility among carbapenem-resistant Enterobacterales in a pilot study in Turkey

Hasan Selcuk Ozger [1], Ebru Evren [2], Serap Suzuk Yildiz [3], Cigdem Erol [4], Fatma Bayrakdar [3], Ozlem Azap [4], Alpay Azap [5], Esin Senol [1]

Affiliations + expand

PMID: 34324428 DOI: 10.1556/030.2021.01525

OXA-48 pozitif %4.6

In Vitro Activities of Ceftazidime-Avibactam and Comparator Antimicrobial Agents Tested against ESBL Producing Urinary E. coli Isolates

Year 2019, Volume 09, Issue 03, 112 - 115, 15.09.2019

Estelle CAİNE Ozlem KOYUNCU OZYURT Gozde ONGUT Kubra KASAROGLU Emre YILDIZ Dilara OGUNC Filiz GUNSEREN Dilek COLAK Ozge TURHAN Betil OZHAK

https://doi.org/10.5799/jmid.614195

%0

Çok Merkezli "Threat" Çalışması

Table 1. MLST and carbapenemases of 187 CRK isolates

	Total	OXA-48-like				OXA48-like[b]/MBL[c]	MBL[c]	KPC-2	KPC-2/MBL[c]
		OXA48	OXA232	OXA244	OXA181				
ST2096	61	2	56	…	…	3[d]	…	…	…
ST101	37	20	…	15	…	2[e]	…	…	…
ST14	28	6	…	1	…	20	1	…	…
ST16	14	8	1	…	3	1	1[g]	…	…
ST307	7	4				…	…	3	…
ST981[a]	6	6				…	…	…	…
ST11	5	3				…	2	…	…
ST15	5	1	…	…	…	1	1	…	2
ST395	5	1	…	…	…	…	4	…	…
Other	19	11	…	1	2	2[f]	2	1	…
Total	187	62	57	17	5	29	11	4	2

MBL oranı%21.3

Abbreviations: MBL, metallo-β-lactamase. [a] All isolates in this MLST are speciated as *Klebsiella variicola*, [b] OXA-48 unless specified otherwise, [c] NDM-1 unless specified otherwise, [d] OXA-48-like type is OXA-232 for all three isolates, [e] OXA-48-like type is OXA-244 for this isolate, [f] NDM type is NDM-5 for one of the two isolates, [g] NDM type is NDM-5

İşler B, Vatansever C ve ark. yayın aşamasında

Table 2. Antibiotic susceptibilities of CRK isolates

Susceptibility (susceptible/total tested)	Total, n (%)	ST2096, n (%)	ST101, n (%)	ST14, n (%)
Colistin	43/187 (23)	11/61 (18)	5/37 (14)	10/28 (36)
Tigecycline	67/157 (43)	12/51 (24)	24/33 (73)	8/26 (31)
Amikacin	45/177 (25)	7/59 (12)	7/32 (22)	5/27 (19)
Gentamicin	42/164 (26)	7/59 (12)	11/26 (42)	3/26 (12)
Trimethoprim-sulfamethoxazole	20/165 (12)	1/60 (2)	6/26 (23)	1/25 (4)
Ceftazidime-avibactam	152/187 (81)	61/61 (100)	37/37 (100)	9/28 (32)

Impact of the ST101 clone on fatality among patients with colistin-resistant *Klebsiella pneumoniae* infection

Fusun Can, Sirin Menekse, Pelin Ispir, Nazlı Atac, Ozgur Albayrak, Tuana Demir, Doruk Can Karaaslan, Salih Nafiz Karahan, Mahir Kapmaz, Ozlem Kurt Azap ... Show more

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 5, May 2018, Pages 1235–1241, https://doi.org/10.1093/jac/dkx532
Published: 03 February 2018 **Article history**

Table 2. Distribution of OXA-48 and NDM-1 among STs

	OXA-48 (*N*=93)	NDM-1 (*N*=22)
ST101 (*N*=68), *n* (%)	65 (96)	0
ST395 (*N*=15), *n* (%)	5 (33)	13 (87)
ST16 (*N*=6), *n* (%)	4 (67)	0
ST147 (*N*=5), *n* (%)	2 (40)	4 (80)
Other STs (*N*=21), *n* (%)	17 (81)	5 (24)

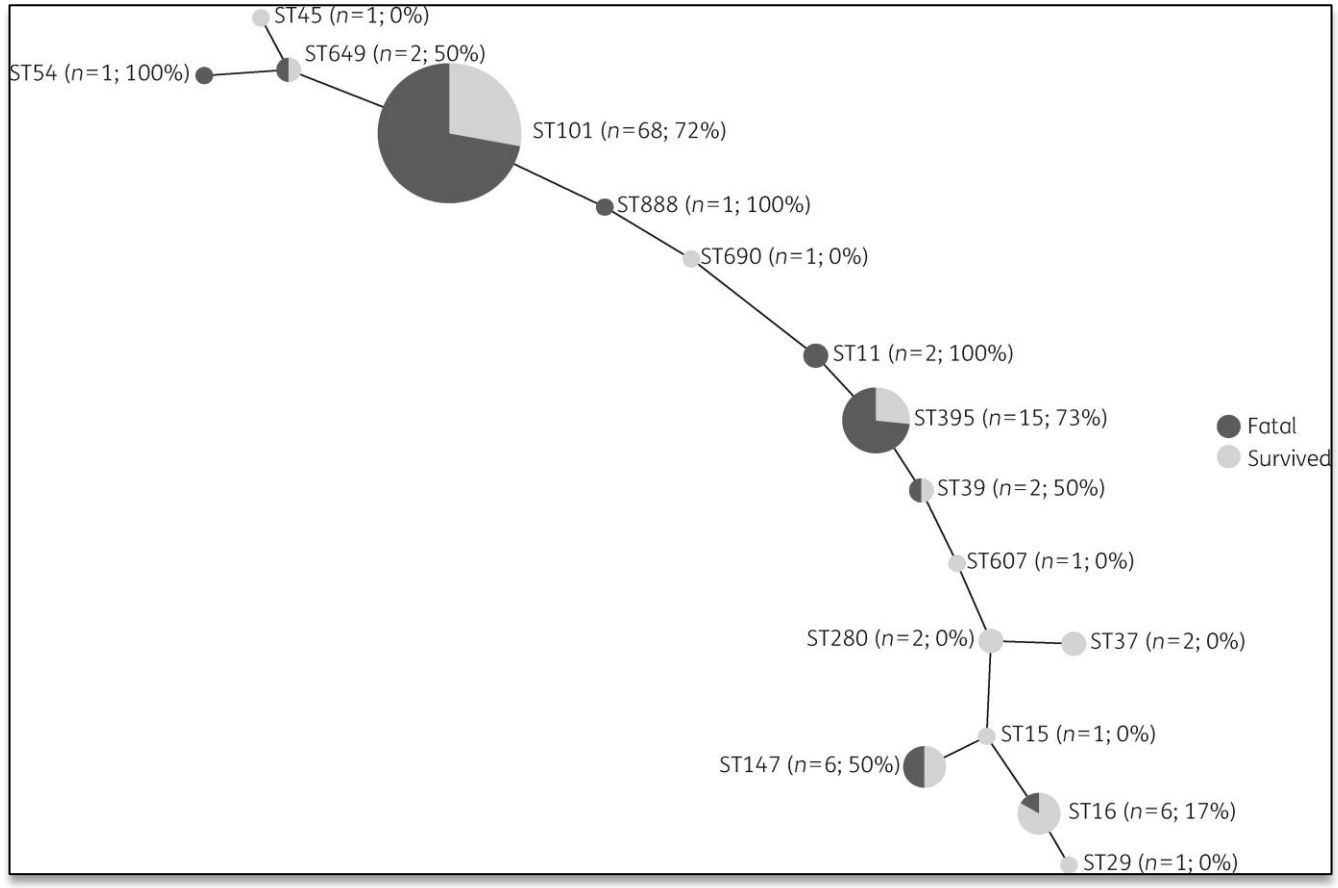


Figure 2. Minimum spanning tree of ColR-Kp by MLST

CRKP enfeksiyonu mortalite ilişkisi

	Univariable analysis			Multivariable analysis[b]		
	HR	CI	P	HR	CI	P
DEMOGRAPHICS						
Age	0.98	0.86-1.13	0.82	…	…	…
Male sex	1.34	0.82-2.20	0.24	…	…	…
SOURCE						
Non-UT source	2.25	0.90-5.60	0.08	1.34	0.52-3.46	0.54
Source control	0.60	0.34-1.04	0.07	0.69	0.39-1.23	0.21
COMORBIDITIES						
Metastatic/hematologic malignancy	1.27	0.73-2.20	0.40	…	…	…
Immunosuppression	1.43	0.83-2.46	0.20	2.14	1.15-4.00	0.02
CCI score	0.97	0.88-1.07	0.56	…	…	…
DISEASE SEVERITY						
ICU at presentation	1.82	1.05-3.16	0.03	0.88	0.41-1.93	0.76
Invasive mechanical ventilation	1.99	1.22-3.25	0.01	1.18	0.58-2.40	0.65
SOFA score (per unit)	1.25	1.17-1.33	0.00	1.24	1.15-1.34	0.000
MICROORGANISM						
Carbapenemase other than single OXA-48-like [a]	1.33	0.78-2.26	0.30	…	…	…
MLST type (reference other)						
ST2096	2.47	1.25-4.86	0.01	1.94	0.95-3.96	0.07
ST101	1.92	0.88-4.22	0.10	1.92	0.84-4.38	0.12
ST14	2.91	1.33-6.36	0.01	1.96	0.88-4.44	0.10
TREATMENT						
Active treatment	0.75	0.46-1.22	0.25	0.71	0.42-1.21	0.21

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

In Vitro Susceptibility of Global Surveillance Isolates of *Pseudomonas aeruginosa* to Ceftazidime-Avibactam (INFORM 2012 to 2014)

Wright W. Nichols,[a]* Boudewijn L. M. de Jonge,[a] Krystyna M. Kazmierczak,[b] James A. Karlowsky,[b] Daniel F. Sahm[b]

AstraZeneca Pharmaceuticals, Waltham, Massachusetts, USA[a]; International Health Management Associates, Inc., Schaumburg, Illinois, USA[b]

P.aeruginosa klinik izolatları n=7.062

CAZ-AVI duyarlılık oranları:

- Toplam %92
- Avrupa %92.6
- Asya/ Güney Pasifik %93.2
- Latin Amerika %88.7
- Orta Doğu/Afrika %91.7

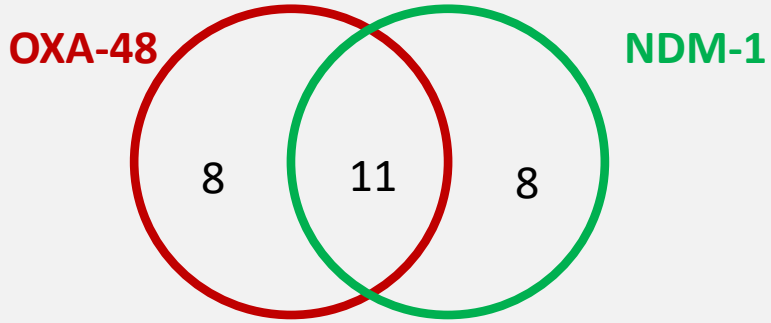
TABLE 1 *In vitro* activities of ceftazidime-avibactam and comparator agents tested against 7,062 *P. aeruginosa* isolates collected in 2012 to 2014 from patients in four geographic regions

Region (no. of isolates)	Antimicrobial agent[a]	MIC_{90} (μg/ml)	% Susceptible[b]
All (7,062)	Ceftazidime-avibactam	8	92.0
	Ceftazidime	64	77.0
	Cefepime	>16	78.3
	Piperacillin-tazobactam	>128	68.6
	Doripenem	>4	74.3
	Meropenem	>8	72.7
	Imipenem	>8	61.4
	Colistin	1	99.5
	Amikacin	32	89.4
	Levofloxacin	>4	71.9
Europe (3,893)	Ceftazidime-avibactam	8	92.6
	Ceftazidime	64	77.4
	Cefepime	16	78.8
	Piperacillin-tazobactam	>128	69.4
	Doripenem	>4	74.4
	Meropenem	>8	72.9
	Imipenem	>8	60.3
	Colistin	1	99.5
	Amikacin	32	89.7
	Levofloxacin	>4	71.3
Asia/South Pacific (1,392)	Ceftazidime-avibactam	8	93.2
	Ceftazidime	64	78.1
	Cefepime	16	80.2
	Piperacillin-tazobactam	>128	71.3
	Doripenem	>4	78.5
	Meropenem	>8	77.4
	Imipenem	>8	67.0
	Colistin	1	99.5
	Amikacin	8	94.4
	Levofloxacin	>4	77.2
Latin America (1,088)	Ceftazidime-avibactam	16	88.7
	Ceftazidime	64	71.5
	Cefepime	>16	73.2
	Piperacillin-tazobactam	>128	62.3
	Doripenem	>4	66.8
	Meropenem	>8	64.9
	Imipenem	>8	57.2
	Colistin	1	99.4
	Amikacin	>32	81.8
	Levofloxacin	>4	64.7
Middle East/Africa (689)	Ceftazidime-avibactam	8	91.7
	Ceftazidime	32	80.8
	Cefepime	16	79.5
	Piperacillin-tazobactam	>128	68.8
	Doripenem	>4	77.1
	Meropenem	>8	74.8
	Imipenem	>8	63.3
	Colistin	1	99.6
	Amikacin	16	90.1
	Levofloxacin	>4	75.9

[a] Colistin was tested in the presence of a final concentration of 0.002% polysorbate 80.
[b] Values are based on CLSI breakpoints, except for ceftazidime-avibactam, for which FDA breakpoints were used.

Kolistin dirençli P.aeruginosa seftazidim avibactam direnci

Kolistin dirençli 27 P.aeruginosa izoaltında karbapenemazlar



IPM=0
KPC-2=0
VIM=0

Kolistin dirençli 27 P.aeruginosa sekans tipleri

	Sequence types					
	235	446	316	3078	3196	novel
Number	13	5	2	3	1	2
Virulence genes						
exoU	-	-	-	-	-	-
exoT	+	+	+	+	+	+
exoS	+	+	+	+	+	+
Toxin A	+	+	+	+	+	+
Alginate	+	+	+	+	+	+
pyochelin	+	+	+	+	+	+
Pyoverdine	+	+	+	+	+	+

Vatansever C, 2021

Kolistin dirençli P.aeruginosa seftazidim avibactam direnci

27 kolistin dirençli P.aeruginosa (Istanbul and Ankara)

	ST235 n (%) 13 (48.1)	Non-ST235 n (%) 14 (51.9)	Total n (%) 27 (100)
30-Day Mortality	10 (76.9)*	6 (42.8%)	16 (59.2%)
Pneumonia	9 (69.1)*	3 (21.4)	12 (44.4)
Wound infection	1 (7.6)	4 (28.5)	5 (18.5)
Urinary infection	3 (23.0)	3 (21.4)	6 (22.2)
Bloodstream infection	4 (30.7)*	-	4 (14.8)

NDM-1 pozitif n=27

	Total n=27	M 1 n=12	M2 n=15
CZA	19 (%70)	11	8
Meropenem	27 (100)	12	15

NDM-1 negatif n=16

	Total n=16	M 1 n=1	M2 n=15
CZA	8 (%50)	0	8
Pip/Tazo	14 (%88)	1	13
Ceftolozane/Tazo	14 (%88)	0	14
Meropenem	16 (100)	1	15

Vatansever C, 2021

Amerikan Hastanesi Enterobacterles türleri ve *Pseudomonas aeruginosa klinik* izolatlarında seftazidim avibaktam direnç oranları

	ESBL pozitif		Karbapenemaz Tarama pozitif		IMP ve/veya MEM Dirençli		CAZ-AVI Dirençli		
	n	%*	n	%*	n	%*	n	%*	%**
***Escherichia coli* (n= 978)**	355	36,2	9	0,9	-	-	4	0,4	
Klebsiella pneumoniae (n= 438)	217	49,5	104	23,7	-	-	28	6,3	26,9
Pseudomonas aeruginosa (n= 296)	-	-	-	-	131	44,2	64	21,6	48,8

Veriler 2020 Aralık - 2021 Aralık arasında bir yıllık döneme aittir. ESBL: EUCAST Seftriakson ve saftazidim disk ile tarama ve kombine disk yöntemi ile doğrulama yapılarak saptanmıştır. Karbapenemaz tarama: EUCAST Meropenem disk tarama kriterlerine göre ve RAPIDEC® CARBA NP ile saptanmıştır. Seftazidim-avibaktam direnci: Disk diffüzyon yöntemi ile saptanmıştır. Tüm izolatla için rutin olarak seftazidim-avibaktam duyarlılığı çalışılmaktadır. n: İzolat sayısı. *: Paydada toplam izolat sayısı olacak şekilde hesaplanmıştır. **: Paydada karbapenem dirençli izolat sayısı olacak şekilde hesaplanmıştır.

Dr.Yeşim Beşli tarafından paylaşılmıştır

Ülkemizden çok merkezli çalışma:

Karbapenenem Dirençli K.pneumoniae'ye Bağlı Kan Enfeksiyonlarında Ceftazidim-avibactam kullanımı

Çok merkezli, retrospektif gözlemsel çalışma (23 Merkez)

Karbapenem dirençli K.pneumoniae bakteremisi olan erişkin hastalar

Ocak 2017-Eylül 2021 tarihleri arasında

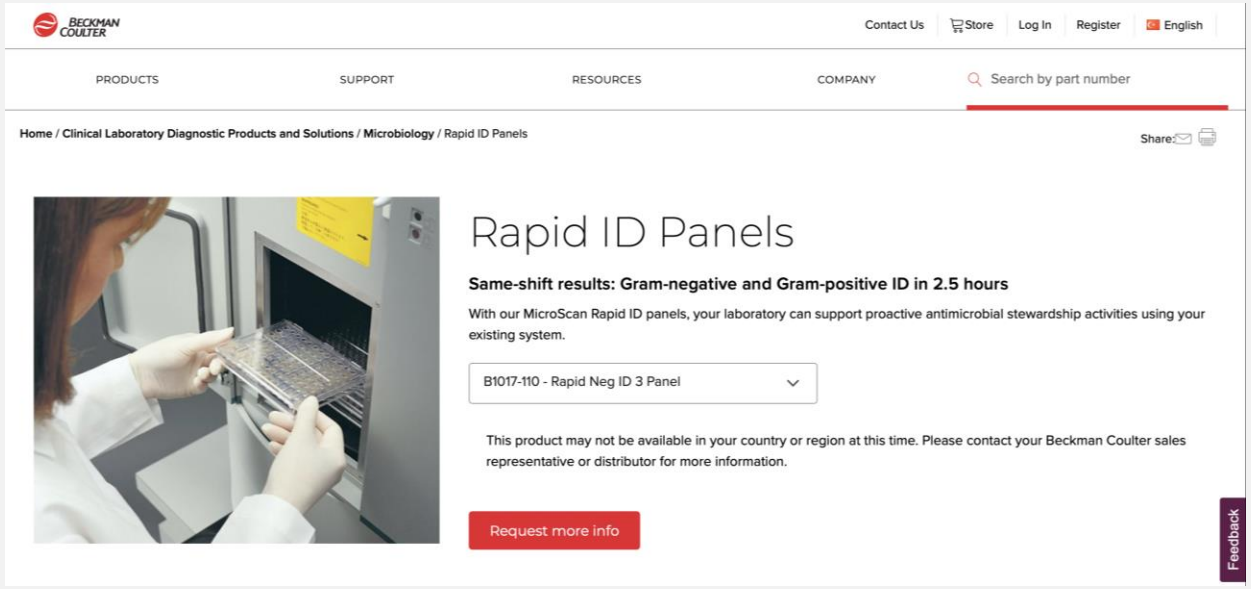
En az 3 gün CAZ-AVI tedavisi verilen hastalar

Okan Derin, Ali Mert, et al.

	Survived n=71	Fatal N=35	p
Male gender	44 (62)	21 (60)	0.845
Mean Age	51 (sd 17)	59 (sd 18)	0.033
Mean Pitt bacteremia score	4.1 (sd 3.2)	7 (sd 2.6)	<0.001
Mean days of starting CZA after culture	2.1 (sd 1.9)	2.9 (sd 1.85)	0.035

Fatal olmayan hastalarda CAZ-AVI tedavisinin erken başlandığı gözlendi

The CA was 100% for *Enterobacterales* and 98.6% for *P. aeruginosa*.



BD Phoenix NMIC-500 Panel CAZ-AVI test performansı

Table 2

AST results for *Enterobacteriaceae*

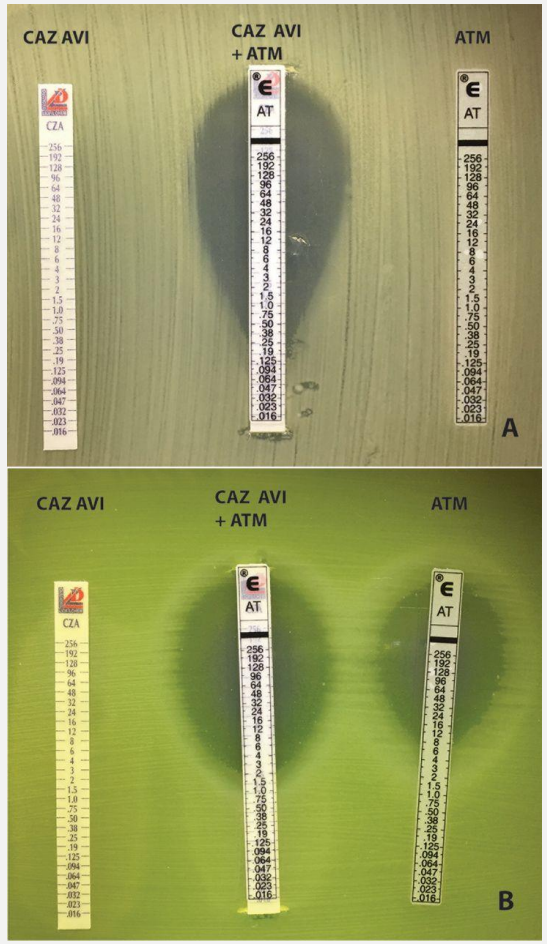
Antimicrobial	N isolates			Phoenix system vs BMD, N (%)				
	S	I	R	EA	CA	mE	ME	VME
Imipenem	212	2	143	358 (87.5)	357 (87.2)	45 (11.0)	7 (1.7)	0 (0)
Meropenem	231	7	132	342 (83.6)	370 (90.5)	28 (6.7)	10 (2.4)	1 (0.2)
Ertapenem	195	4	188	402 (98.3)	387 (94.6)	21 (5.1)	1 (0.2)	0 (0)
Ceftazidime	125	10	253	402 (98.3)	388 (94.9)	18 (4.4)	1 (0.2)	2 (0.5)
Ceftazidime/Avibactam	317	-	82	358 (87.5)	399 (97.6)	0 (0)	6 (1.5)	4 (0.9)

Abbreviations: AST, antimicrobial susceptibility testing; BMD, broth microdilution; EA, essential agreement; CA, categorical agreement; S, susceptible; I, intermediate; R, resistant; mE, minor error; ME, major error; VME, very major error.

Park et al. Ann Lab Med,2019

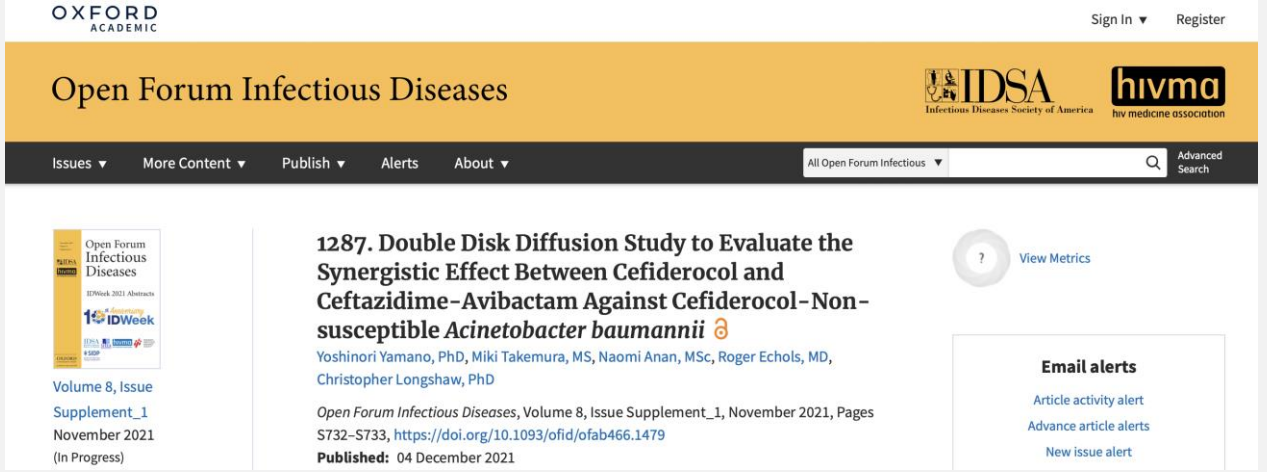
Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Authors: Benjamin Davido, Lesly Fellous, Christine Lawrence, Virginie Maxime, Martin Rottman, and Aurélien



59 yaşında erkek hasta, kateter ilişkili K.pneumoniae enfeksiyonu
Kolistin ve karbapenem dirençli,
OXA-48 ve NDM-1 pozitif
CAZ-AVI ve ATM MİK>256 mg/L
10 günlük tedavi kültür negatif

55 yaşında erkek hasta, myestenia ve pnömoni
Karbapenem dirençli P.aeruginosa
NDM-1 ve AMPC pozitif
CAZ-AVI ve ATM MİK>256 mg/L
6 hafta tedavi ile kür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Volume 8, Issue Supplement_1
November 2021
(In Progress)
1287. Double Disk Diffusion Study to Evaluate the Synergistic Effect Between Cefiderocol and Ceftazidime-Avibactam Against Cefiderocol-Non-susceptible Acinetobacter baumannii
Yoshinori Yamano, PhD, Miki Takemura, MS, Naomi Anan, MSc, Roger Echols, MD, Christopher Longshaw, PhD
Open Forum Infectious Diseases, Volume 8, Issue Supplement_1, November 2021, Pages S732–S733, https://doi.org/10.1093/ofid/ofab466.1479
Published: 04 December 2021
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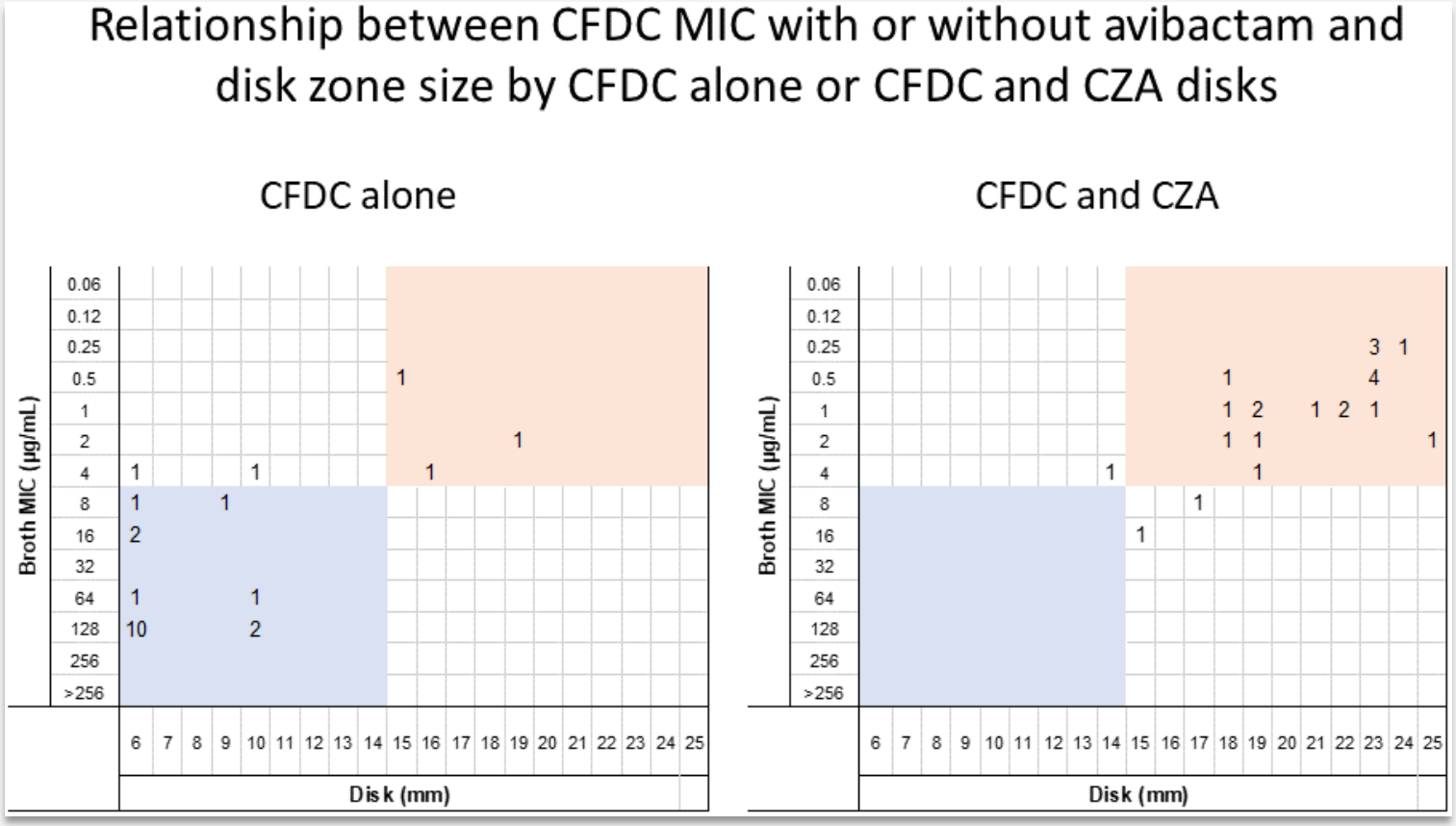
Relationship between CFDC MIC with or without avibactam and disk zone size by CFDC alone or CFDC and CZA disks
CFDC alone
CFDC and CZA
Broth MIC (µg/mL)
0.06
0.12
0.25
0.5
1
2
4
8
16
32
64
128
256
>256
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Disk (mm)

Seftazidim Avibaktam Direnç Mekanizmaları

- Dış membran permiabilite azalması
- KPC-3 kopya sayısı yüksek
- Karbapenemaz mutasyonları
- Effluks pompa mutasyonları

Table 2
Reports of possible resistance mechanisms against ceftazidime-avibactam (CAZ-AVI) in different pathogens.

Ambler class classification	β-Lactamases	Pathogen	Mechanism
A	KPC-3 mutation	*K. pneumoniae*	D179Y: Tyr-for-Asp acid substitution at amino acid position 179 within the KPC-3Ω loop [58,62,63]
		K. pneumoniae	V240G: Gly for Val substitution at amino acid position 240 [58]
		K. pneumoniae	T243M: Met for Thr substitution at position 243 [60]
		K. pneumoniae	A177E: Glu for Ala substitutions at KPC-3 177 positions 177 [59]
		K. pneumoniae	165–166 EL: Glu and Leu insertion between positions 165 and 166 [60]
		K. pneumoniae	V240A: Ala for Val substitution at amino acid position 240 [61]
	KPC-2 mutation	*K. pneumoniae*	L169P: Pro for Leu substitution at amino acid position 169 [66]
		E. coli	Asn for Asp substitution at amino acid position 179 [67]
		E. coli	D179Y: Tyr for Asp acid substitution at amino acid position 179 [65]
	CTX mutation	*E. coli*	CTX-M-15 mutation: Asp for Tyr substitution at amino acid position 182 [68]; L169Q and S130G: Gln for Leu substitution at amino acid position 169 and Gly for Ser substitution at amino acid position 130 [70]
		K. pneumoniae	CTX-M-14 mutation: Pro for Ser substitution at amino acid position 170; Thr for Ile substitution at amino acid position 264 [69]
	SHV mutation	*E. coli*	SHV-Ser130Gly: lack of a hydroxyl group at the 130 position slows carbamylation of the enzyme by avibactam [71].
B	Zn^{2+}-dependent metalloenzymes	*E. coli*	MBLs belonging to subclasses B1, B2 and B3 all catalyse avibactam hydrolysis [55] (e.g. VIM, imipenemase [IMP], NDM [23,103]).
		K. pneumoniae	
		P. aeruginosa	
C	AmpC mutation	*P. aeruginosa*	The changes in the Ω loop are expected to influence both ceftazidime hydrolysis and avibactam inhibition [72]. Mutations in positions such as amino acids 168, 176, 309–314 and 366 lead to non-susceptibility;
		C. freundii	
		E. cloacae	Arg168His (and Gly176Arg/Asp) raised CAZ-AVI MICs [68].
		E. coli	Structural alterations in the R2 binding site and H-9 and H-10 helices, which are secondary structures surrounding the R2 binding site [74]
		E. cloacae	CHE: contains a six-residue deletion in the H-10 helix in close proximity to the active site [73]
		C. freundii	Asn for Tyr substitution at amino acid position 346 or a Tyr for Ser substitution at amino acid position 150, which result in a steric clash with the sulphate group of avibactam, thus influencing the binding affinity of the inhibitor [75]
		E. coli	CMY-6: Tyr for Cys substitution at amino acid position 150 [75]
		K. aerogenes	CMY-10: Asn for Ile substitution in helix H-11 position 346 [74]
D	OXA-2 mutation	*P. aeruginosa*	OXA-539: duplication of the key residue Asp149 [107]
	OXA-48 mutation	*E. coli*	P68A and Y211S: Ala for Pro substitution at amino acid position 68 and Ser for Tyr substitution at amino acid position 211 coexist [76].
	OXA-40, 66, 69, 88, 93–96, 206 [77]	*A. baumannii*	

KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration.

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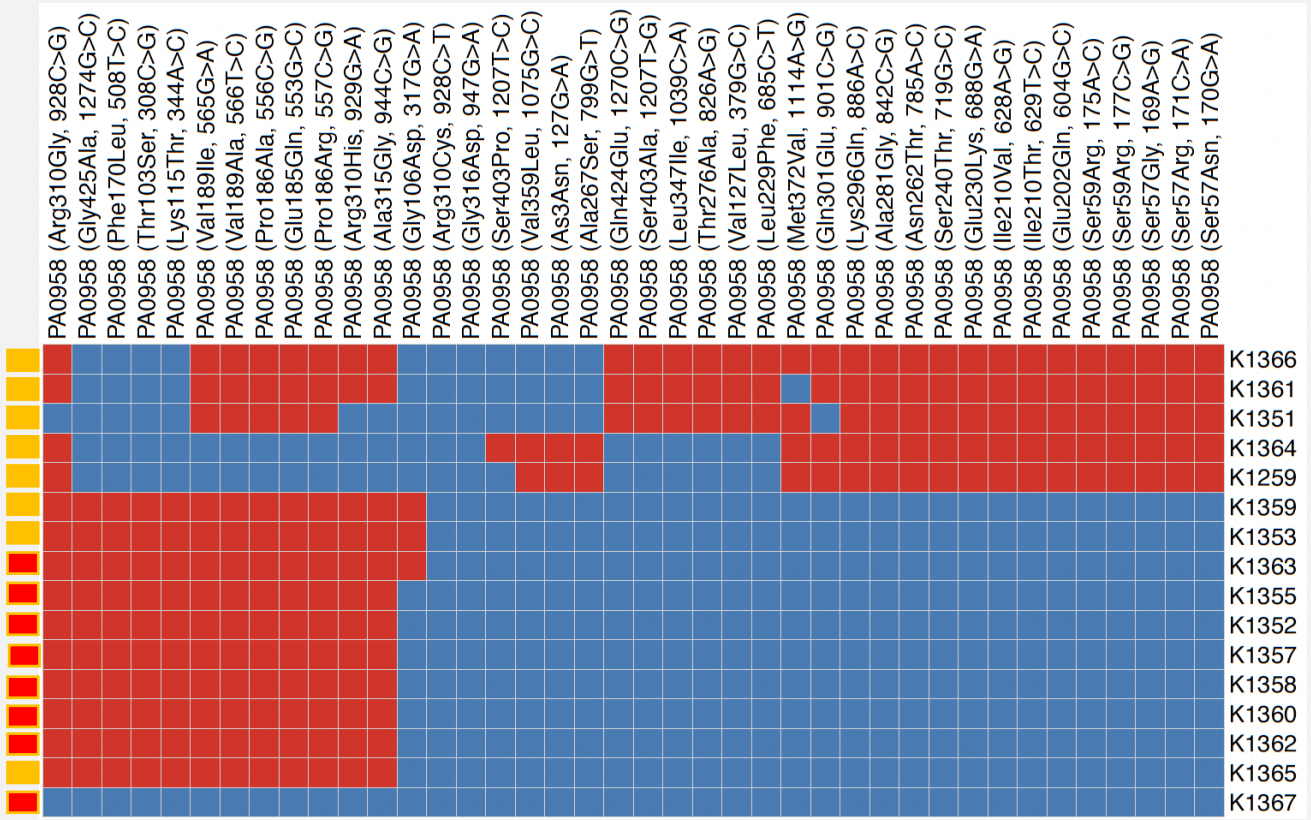
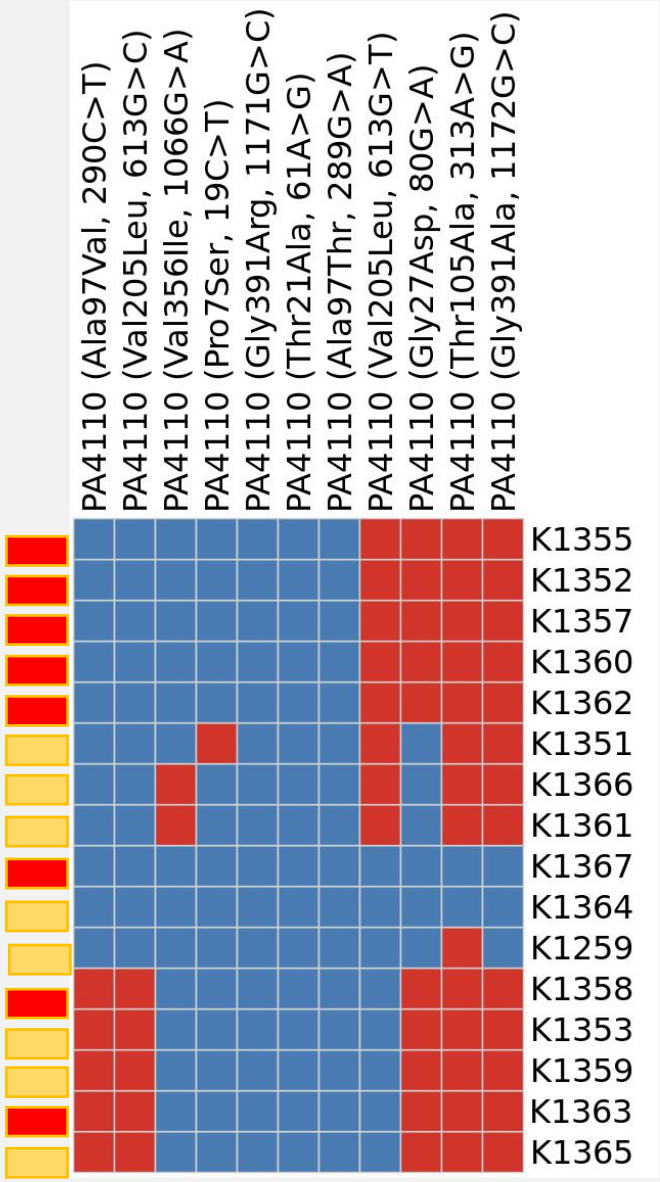
Kolistin Dirençli P.aeruginosa CAZ direnç Mekanizmaları



oprD



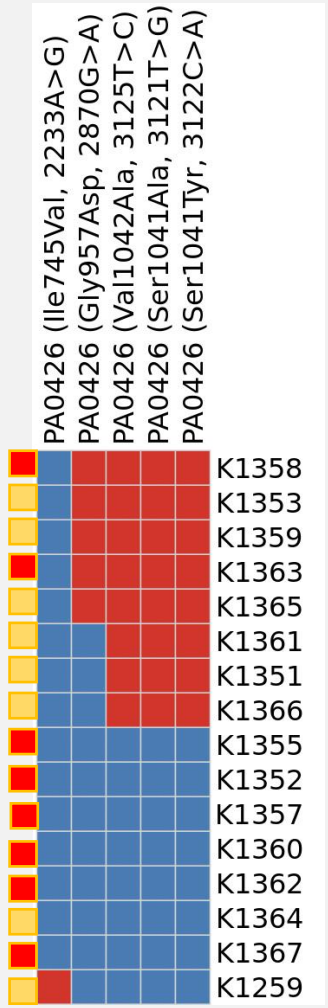
ampC

CZA duyarlı

CZA dirençli

Kolistin Dirençli P.aeruginosa CAZ direnç Mekanizmaları

mexA mutasyon yok



mexB

Sonuç olarak,

- XDR- MDR Enterobactereles enfeksiyonlarında CAZ-AVI uygun seçenek
- Duyarlılık test sonucunun erken elde edilmesi klinik yararı artırıyor
- Karbapenemaz moleküler testleri yararlı, ancak fenotipik testler çalışılmalı
- Direnç gelişiminde karbapenemaz ve dış membran geçirgenliği önemli
- Çok merkezli, laboratuvar ve klinik verilerin harmanlandığı büyük ölçekli çalışmalara ihtiyaç var


Teşekkürler….