Karbapenem Dirençli *Enterobacteriaceae* İnfeksiyonlarında Tedavi Yaklaşımı

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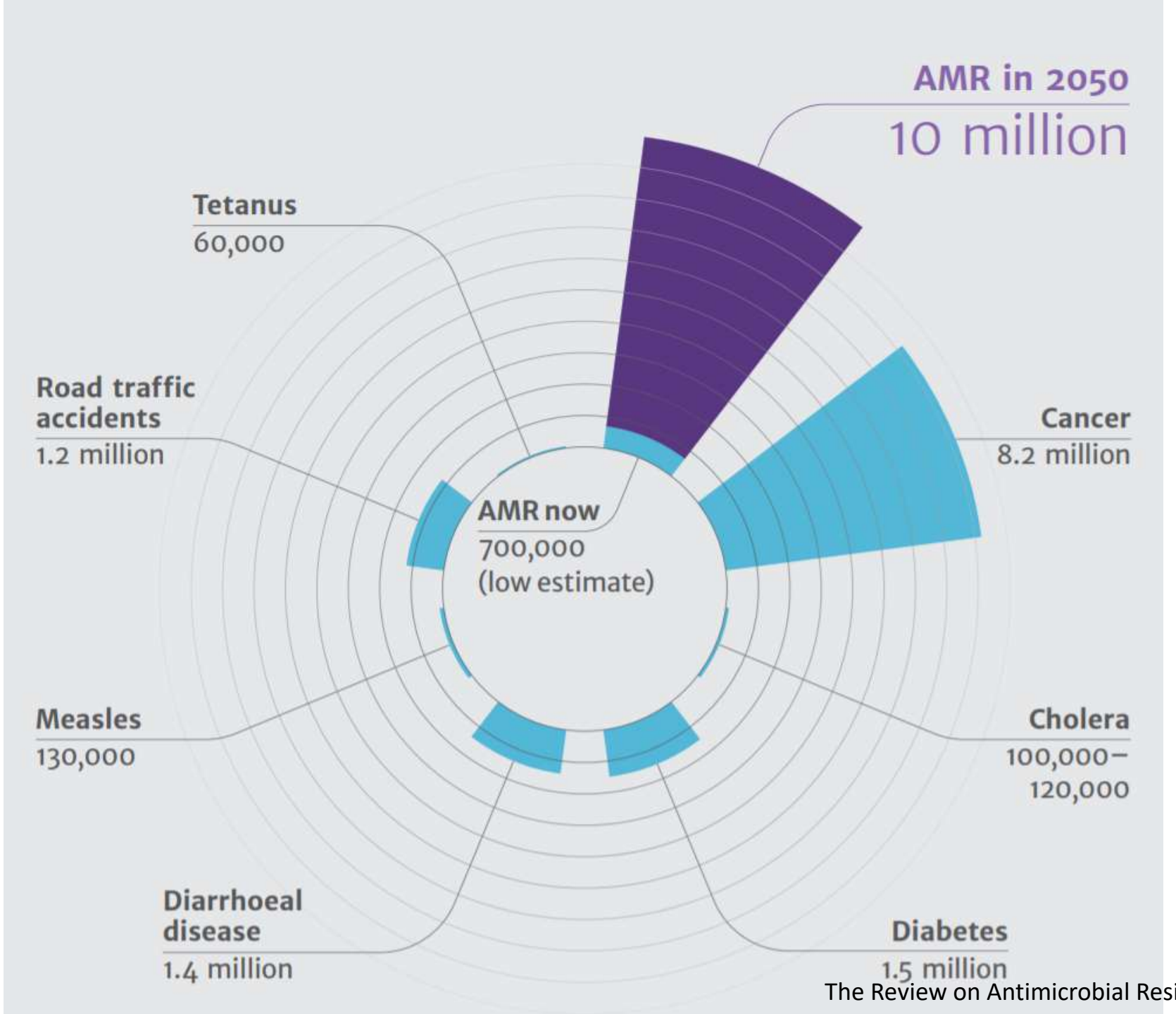
KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

ONDOKUZ MAYIS ÜNİVERSİTESİ

ADÇG
KLİMİK DERNEĞİ ANTİBİYOTİK DİRENCİ ÇALIŞMA GRUBU



The Review on Antimicrobial Resistance, Chaired by Jim O'Neill

DSÖ İlk Kez Acil
Yeni Antibiyotik Gerektiren
Bakteriler Listesi Yayımladı

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Karbapenem Dirençli *Enterobacteriaceae*

USHİESA etken dağılımı ve antibiyotik direnç raporu 2018

	K. pneumoniae %	*E.coli %*
Meropenem	57	14
Amikasin	43	19
Kolistin	27	8
Piperasilin-tazobaktam	81	44
Siprofloksasin	75	65

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Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Rapid emergence of colistin resistance and its impact on fatality among healthcare-associated infections

M. Aydın [a,*], Ö. Ergönül [b], A. Azap [c], H. Bilgin [d], G. Aydın [c,e], S.A. Çavuş [f], Y.Z. Demiroğlu [g], H.E. Alışkan [h], O. Memikoğlu [c], Ş. Menekşe [i], Ş. Kaya [j], N.A. Demir [k], İ. Karaoğlan [l], S. Başaran [m], Ç. Hatipoğlu [n], Ş. Erdinç [n], E. Yılmaz [o], A. Tümtürk [p], Y. Tezer [p], H. Demirkaya [q], Ş.E. Çakar [r], Ş. Keske [b], S. Tekin [b], C. Yardımcı [s], Ç. Karakoç [t], P. Ergen [u], Ö. Azap [q],

Table I

Antibiotic resistance rates in 1556 episodes of healthcare-associated Gram-negative bacteraemia

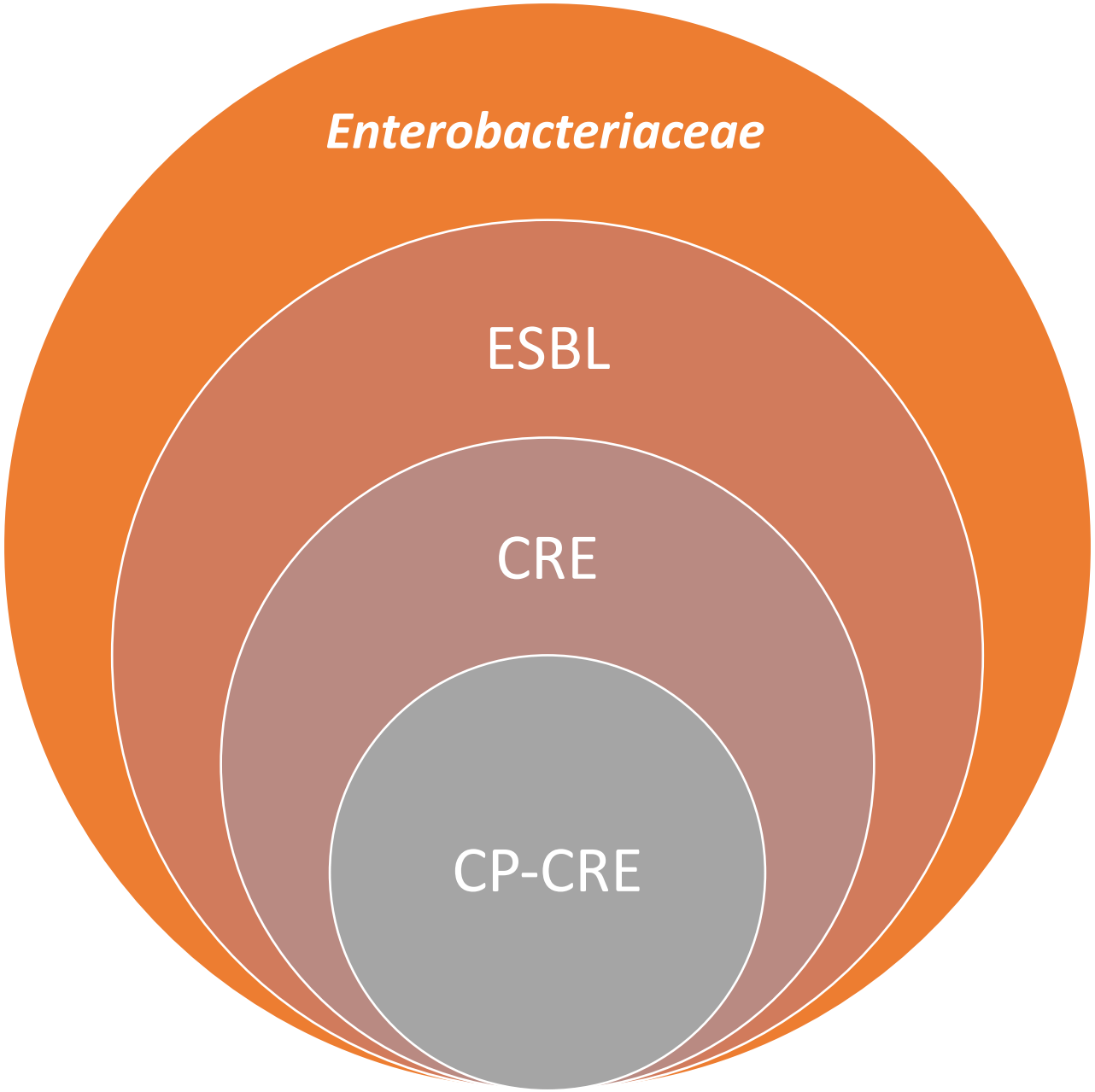
Species	*N* (%) of isolates that were resistant to:				
	Carbapenems	Fluoroquinolones	Third-generation cephalosporins	Aminoglycosides	Colistin
Acinetobacter baumannii N = 437	401 (91.8)	389 (89.0)	410 (93.8)	310 (70.9)	9 (2.1)
Klebsiella pneumoniae N = 416	216 (51.9)	266 (63.9)	320 (76.9)	200 (48.1)	67 (16.1)
Escherichia coli N = 339	34 (10.0)	189 (55.8)	203 (59.9)	103 (30.4)	3 (0.9)
Pseudomonas aeruginosa N = 205	88 (42.9)	102 (49.8)	103 (50.2)	65 (31.7)	18 (8.8)
Enterobacter cloacae N = 159	37 (23.3)	46 (28.9)	59 (37.1)	51 (32.1)	9 (5.7)

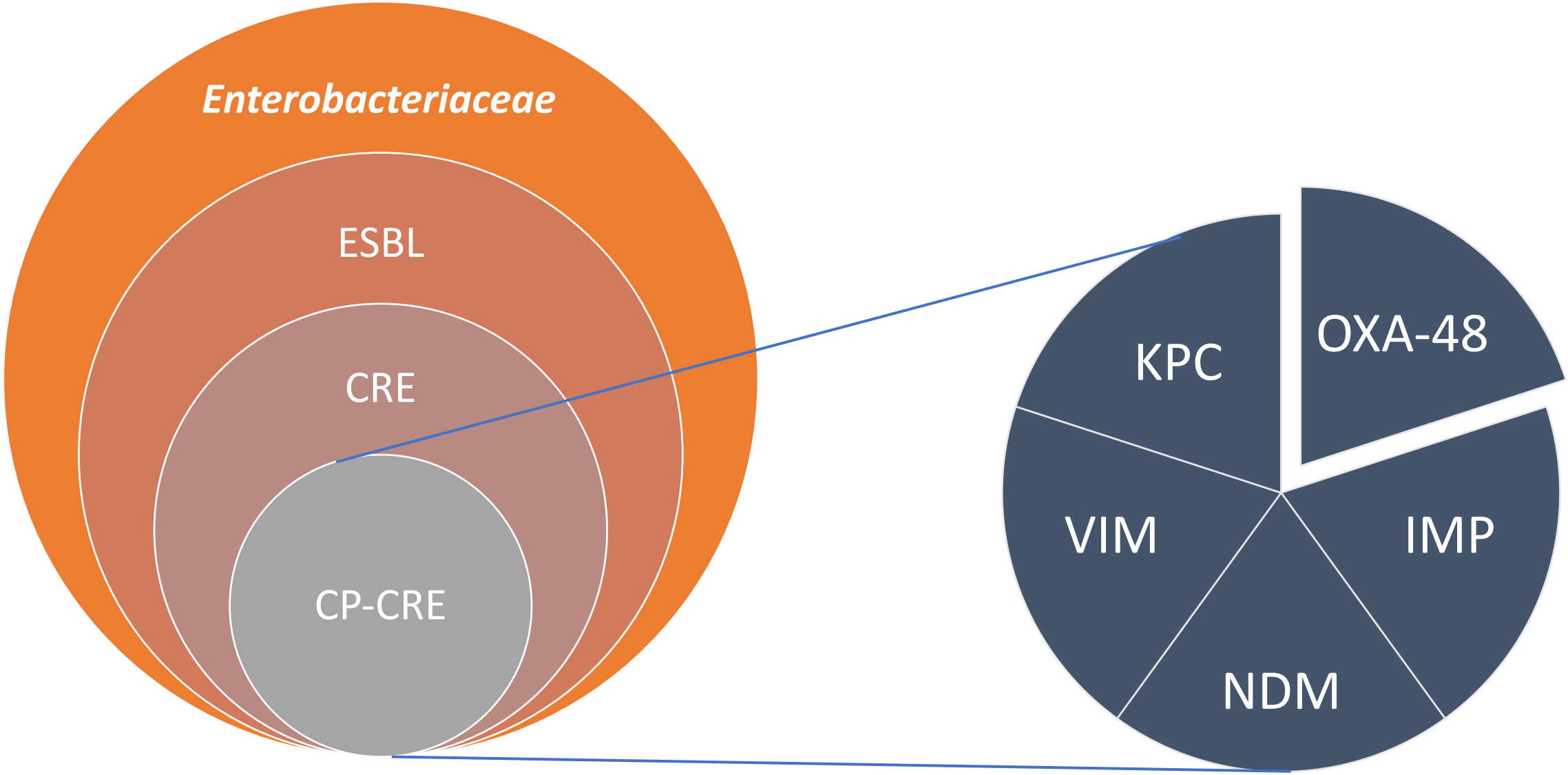
Enterobactericeada 3 majör mekanizma direnç gelişiminden sorumludur.

Efflux pompa

Porin mutasyonu

Enzim üretimi- karbapenem direncinden en önemli mekanizmadır.


Enterobacteriaceae
ESBL
CRE
CP-CRE


Enterobacteriaceae
ESBL
CRE
CP-CRE
KPC
OXA-48
VIM
IMP
NDM

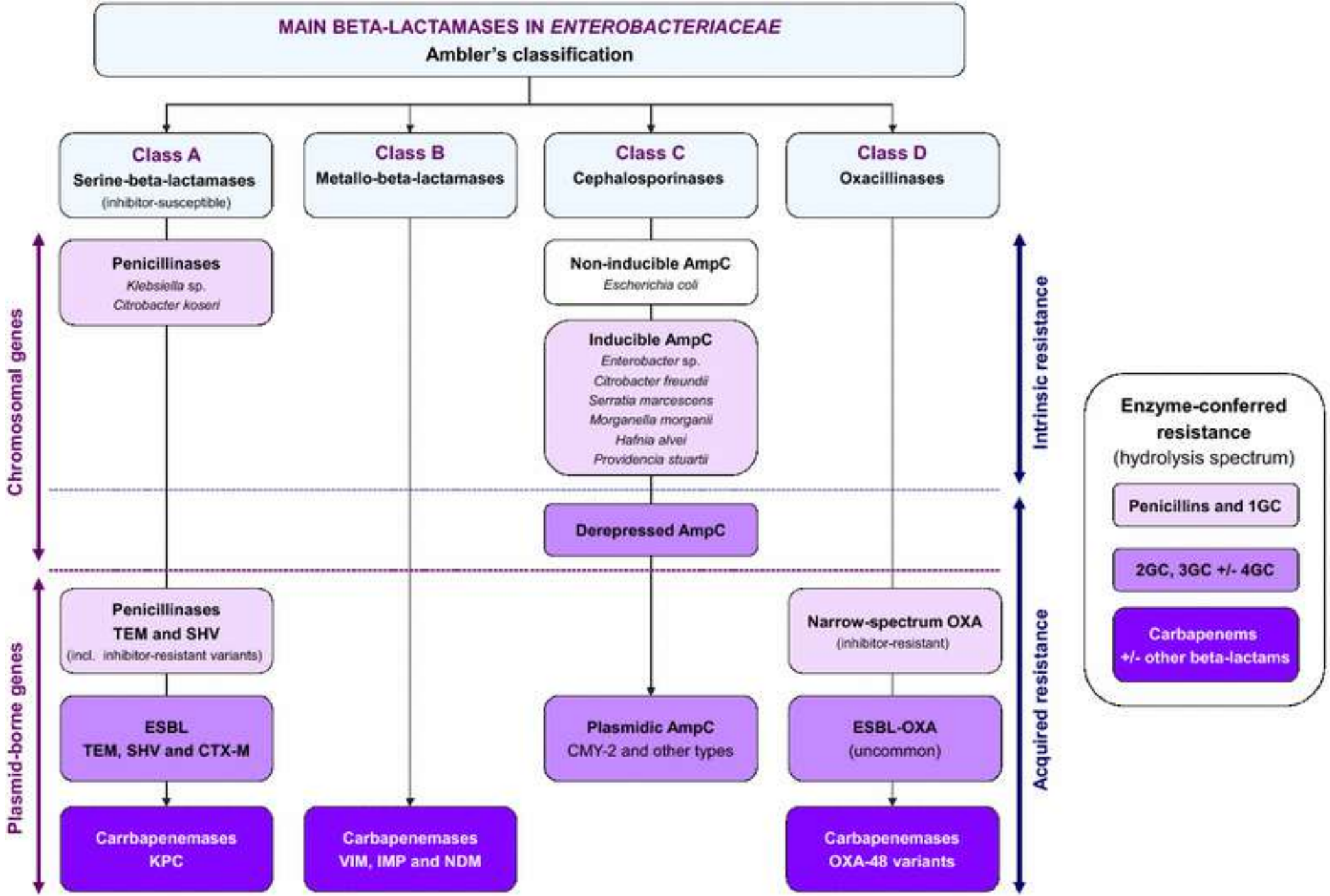

MAIN BETA-LACTAMASES IN ENTEROBACTERIACEAE
Ambler's classification
Class A
Serine-beta-lactamases
(inhibitor-susceptible)
Class B
Metallo-beta-lactamases
Class C
Cephalosporinases
Class D
Oxacillinases
Penicillinases
Klebsiella sp.
Citrobacter koseri
Non-inducible AmpC
Escherichia coli
Inducible AmpC
Enterobacter sp.
Citrobacter freundii
Serratia marcescens
Morganella morganii
Hafnia alvei
Providencia stuartii
Derepressed AmpC
Penicillinases
TEM and SHV
(incl. inhibitor-resistant variants)
Narrow-spectrum OXA
(inhibitor-resistant)
ESBL
TEM, SHV and CTX-M
Plasmidic AmpC
CMY-2 and other types
ESBL-OXA
(uncommon)
Carrbapenemases
KPC
Carbapenemases
VIM, IMP and NDM
Carbapenemases
OXA-48 variants
Chromosomal genes
Plasmid-borne genes
Intrinsic resistance
Acquired resistance
Enzyme-conferred resistance
(hydrolysis spectrum)
Penicillins and 1GC
2GC, 3GC +/- 4GC
Carbapenems
+/- other beta-lactams

Table 2. β-Lactamase Inhibitor Combinations.

Inhibitor	Spectrum	Combination Antibiotics
Clavulanic acid[28-30]	Class A narrow spectrum	Amoxicillin
	Class A ESBLs	Ticarcillin
Tazobactam[6,39]	Class A narrow spectrum	Piperacillin
	Class A ESBLs	Ceftolozane
	Some class C enzymes	
Sulbactam[19,35,37]	Class A narrow spectrum	Ampicillin
	Class A ESBLs	Piperacillin
		Cefoperazone
Avibactam[46-48]	Class A narrow spectrum	Ceftaroline
	Class A ESBLs	Ceftazidime
	Class A carbapenemases	Aztreonam
	Some class C and class D enzymes	
MK-7655[75,76]	Class A narrow spectrum	Imipenem
	Class A ESBLs	
	Class A carbapenemases	
	Some class C enzymes	
RPX7009[83,84,85]	Class A narrow spectrum	Biapenem
	Class A ESBLs	
	Class A carbapenemases	
	Some class C enzymes	

Abbreviation: ESBL, extended-spectrum β-lactamase.

Özgün Çalışma/Original Article

Mikrobiyol Bul 2016; 50(1): 21-33

doi: 10.5578/mb.10695

Türkiye'de 2014 Yılı İçinde İzole Edilen Karbapeneme Dirençli *Escherichia coli* ve *Klebsiella pneumoniae* İzolatlarında Karbapenemaz Varlığının Araştırılması*

Investigation of Carbapenemases in Carbapenem-Resistant *Escherichia coli* and *Klebsiella pneumoniae* Strains Isolated in 2014 in Turkey

Aslı ÇAKAR[1], Yakut AKYÖN[1], Deniz GÜR[1], Onur KARATUNA[2], Dilara ÖĞÜNÇ[3], Betil ÖZHAK BAYSAN[3] Nilay ÇÖPLÜ[4], Mustafa ÇAĞATAY[4], Abdullah KILIÇ[5], Mehmet BAYSALLAR[5], Zahir BAKICI[6], Cem ÇELİK[6], Zeynep GÜLAY[7], Şöhret AYDEMİR[8], Alper TÜNGER[8], Hüseyin KILIÇ[9], Barış Derya ERÇAL[9], Zulal AŞÇI TORAMAN[10], Yasemin ZER[11], Ayşe BÜYÜKTAŞ[11], Selma AY[12], Zerrin AKTAŞ[13], Çiğdem KAYACAN[13], Gülçin BAYRAMOĞLU[14], Faruk AYDIN[14], Devrim DÜNDAR[15], Ufuk HASDEMİR[16], Ramazan AYAŞ[16], Keramettin YANIK[17], Murat GÜNAYDIN[17], Hüseyin GÜDÜCÜOĞLU[18],

Tablo III. *Karbapenemaz Varlığı Saptanan K.pneumoniae ve E.coli Izolatında Karbapenemaz Tiplerinin Dağılımı (n= 143)*

	E.coli	*K.pneumoniae*	Toplam
Karbapenemaz geni	Sayı (%)	Sayı (%)	Sayı (%)
OXA-48	18 (94.7)	103 (83.1)	121 (84.6)
NDM	1 (5.3)	8 (6.5)	9 (6.3)
VIM	0	4 (3.2)	4 (2.8)
IMP	0	2 (1.6)	2 (1.4)
OXA-48 + NDM	0	3 (2.4)	3 (2.1)
OXA-48 + VIM	0	3 (2.4)	3 (2.1)
VIM + NDM	0	1 (0.8)	1 (0.7)
Toplam	19 (100)	124 (100)	143 (100)

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	Hospitals submitting carbapenem non-susceptible *K pneumoniae* isolates (n)	Number of submitted carbapenem non-susceptible *K pneumoniae* isolates	Confirmed carbapenemase-producing *K pneumoniae* isolates					Other (n, %)*
			KPC (n, %)	NDM (n,%)	OXA-48-like (n, %)	VIM (n, %)	Total (n, %)	
Albania	3	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Austria	6	15	6 (40·0)	2 (13·3)	2 (13·3)	0 (0)	10 (66·7)	5 (33·3)
Belgium	11	48	13 (27·1)	2 (4·2)	18 (37·5)	0 (0)	33 (68·8)	15 (31·3)
Bulgaria	3	4	0 (0)	2 (50·0)	0 (0)	0 (0)	2 (50·0)	2 (50·0)
Croatia	14	48	1 (2·1)	0 (0)	1 (2·1)	5 (10·4)	7 (14·6)	41 (85·4)
Cyprus	1	1	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)
Czech Republic	5	26	0 (0)	1 (3·8)	1 (3·8)	0 (0)	2 (7·7)	24 (92·3)
Denmark	3	8	1 (12·5)	3 (37·5)	2 (25·0)	0 (0)	6 (75·0)	2 (25·0)
Estonia	1	9	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (100)
Finland	1	1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
France	11	27	1 (3·7)	0 (0)	10 (37·0)	0 (0)	11 (40·7)	16 (59·3)
Germany	13	36	8 (22·2)	2 (5·6)	12 (33·3)	0 (0)	22 (61·1)	14 (38·9)
Greece	10	86	56 (65·1)	12 (14·0)	2 (2·3)	9 (10·5)	79 (91·9)	7 (8·1)
Turkey	17	124	0 (0)	9 (7·3)	98 (79·0)	5 (4·0)	112 (90·3)	12 (9·7)
UK-England and Northern Ireland	15	47	14 (29·8)	3 (6·4)	7 (14·9)	1 (2·1)	25 (53·2)	22 (46·8)
UK-Scotland	4	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Total	251	1203	379 (31·5)	93 (7·7)	310 (25·8)	68 (5·7)	850 (70·7)	353 (29·3)

Lancet Infect Dis 2016
Published Online
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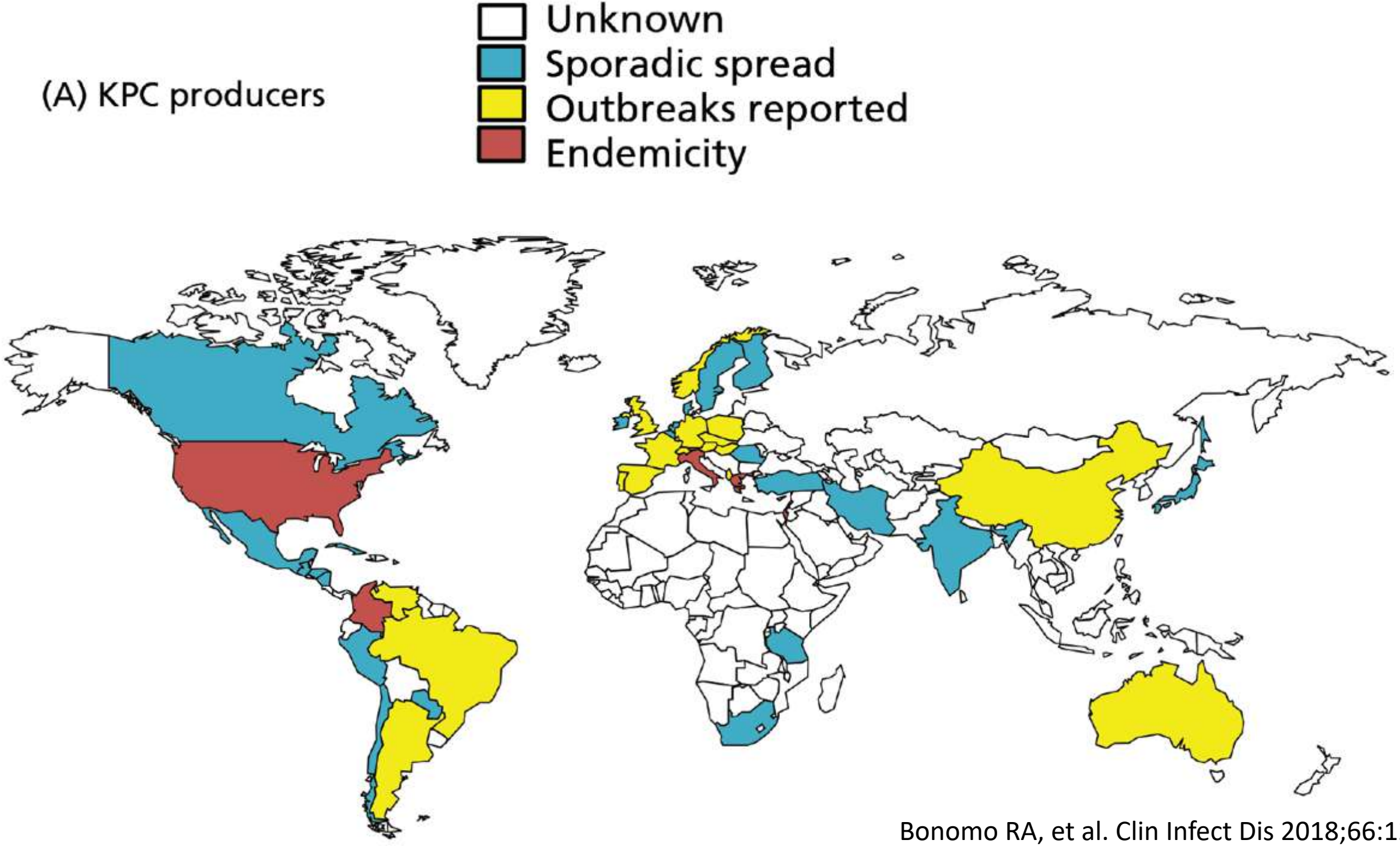
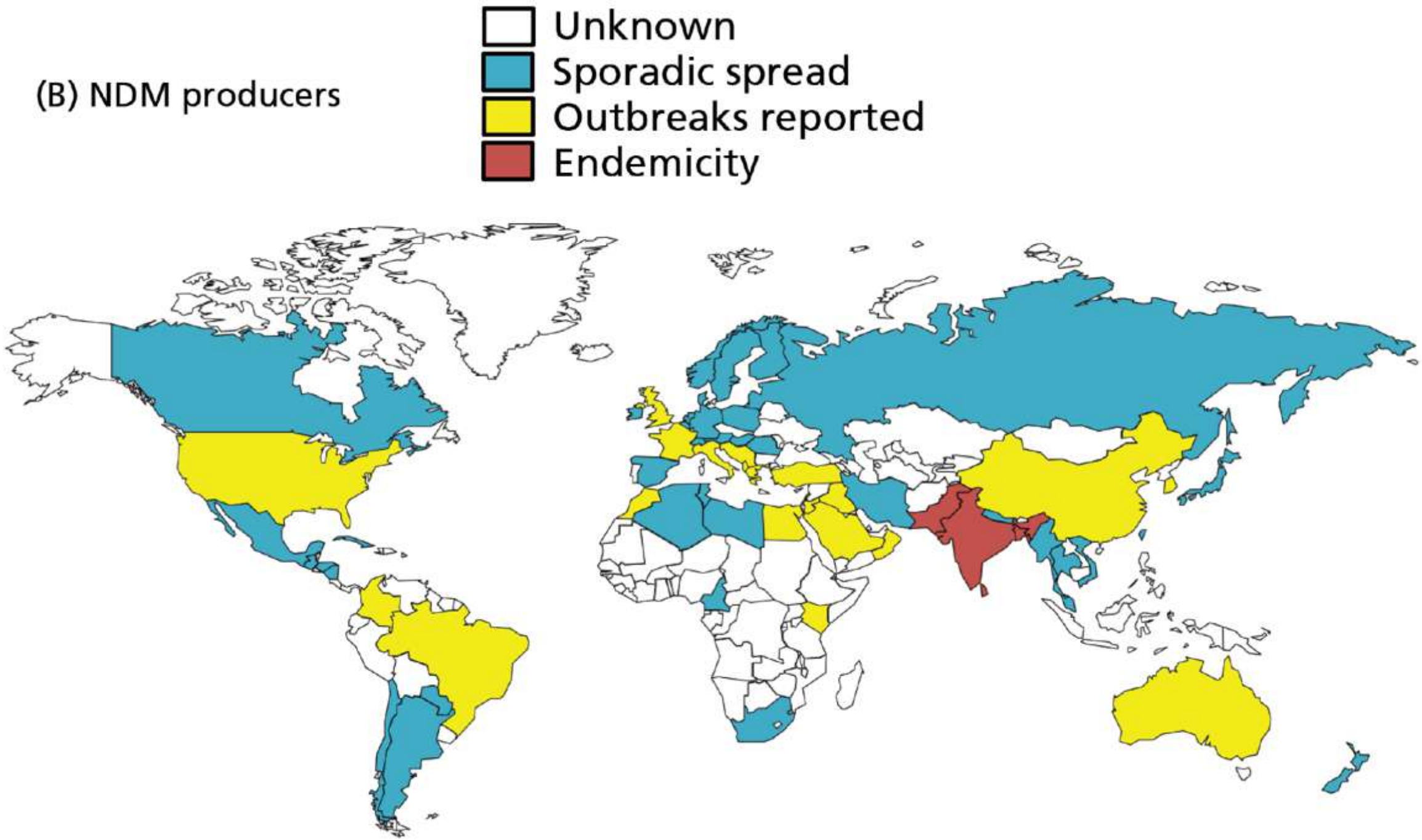
http://dx.doi.org/10.101
S1473-3099(16)30257-

(A) KPC producers



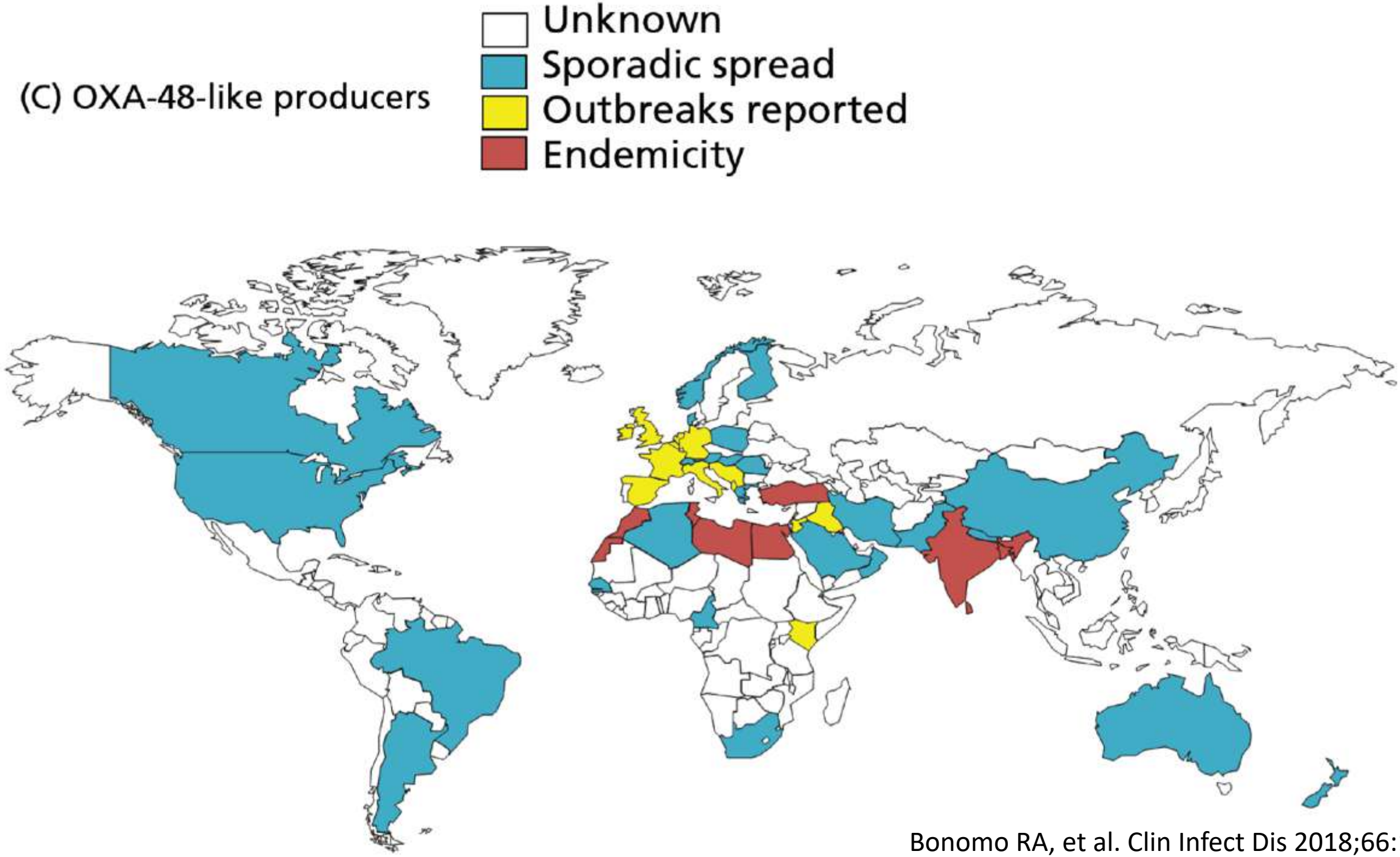
Bonomo RA, et al. Clin Infect Dis 2018;66:1290

(B) NDM producers



Bonomo RA, et al. Clin Infect Dis 2018;66:1290

(C) OXA-48-like producers



Bonomo RA, et al. Clin Infect Dis 2018;66:1290

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Short report

Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality

Ö. Ergönül [a,*], M. Aydin [b], A. Azap [c], S. Başaran [d], S. Tekin [a], Ş. Kaya [e], S. Gülsün [e],

Değişkenler	Odds ratio	95%CI	p
>70 yaş	2	1.22-3.51	0.006
Santral venöz kateter	2.1	1.09-4.07	0.025
Ventilatör ilişkili pnömoni	1.9	1.1-3.16	0.02
Karbapenem direnci	1.8	1.11-2.95	0.016
APACHE II skoru	1.1	1.07-1.13	<0.001

Tedavi seçenekleri

Kolistin

Tigesiklin

Fosfomisin

Aminoglikozidler

Karbapenemler

Seftazidim-avibactam

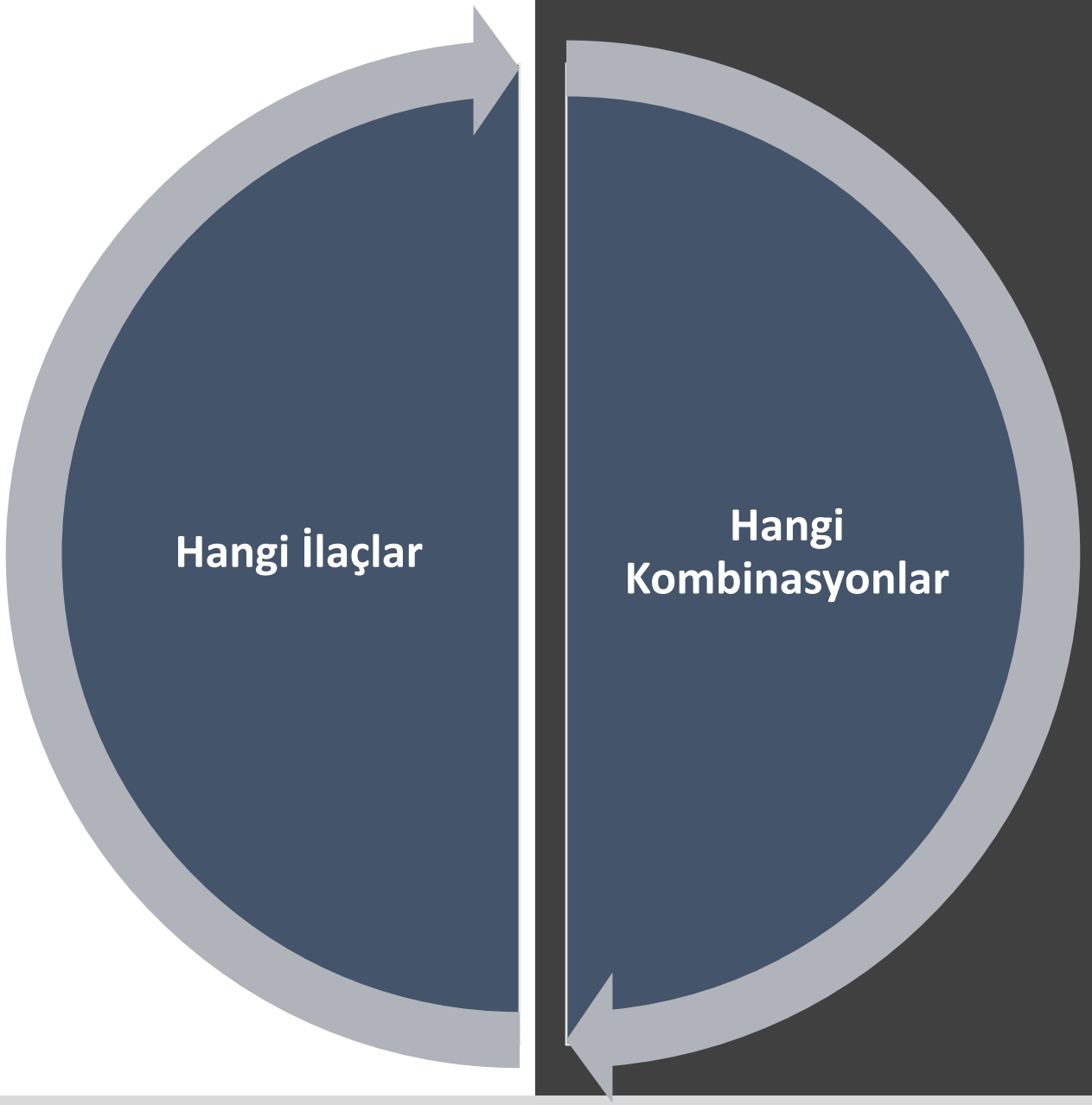
Meropenem-vaborbaktam

Plazomisin

Eravasiklin

İmipenem-relebactam

Sefiderakol


Hangi İlaçlar
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journal homepage: www.clinicalmicrobiologyandinfection.com

ABD, Fransa, Yunanistan, İsrail, İtalya, Kosova, Slovenya, İspanya

Ocak-Haziran 2017 arasında toplam 8 ülke ve 115 hastane katılmış

Original article

Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals

Most frequent antibiotic regimens for targeted treatment for infections caused by carbapenem-resistant *Enterobacteriaceae* [a]

Total $N = 114$	cUTI	Pneumonia	IAI	SSTI	CNSI	Bacteraemia
Monotherapy ($N = 57$, 50%)						
POL	20 (35.1)	18 (31.6)	10 (17.5)	12 (21.2)	7 (12.3)	17 (29.8)
TIG	5 (8.8)	9 (15.8)	20 (35.1)	20 (35.1)	3 (5.3)	8 (14)
AMG	40 (70.2)	6 (10.5)	8 (14)	7 (12.3)	3 (5.3)	14 (24.6)
FOS	19 (33.3)	1 (1.8)	1 (1.8)	0 (0)	3 (5.3)	3 (5.3)
CAZ/AVI	20 (35.1)	16 (28.1)	17 (29.8)	16 (28.1)	5 (8.8)	17 (29.8)
Double combination therapy ($N = 105$, 92.1%)						
POL + TIG	13 (10)	43 (41)	61 (58.1)	40 (38.1)	9 (8.6)	34 (32.4)
POL + CARB	53 (50.5)	63 (60)	52 (49.5)	35 (33.3)	52 (49.5)	67 (63.9)
TIG + CARB	6 (5.7)	24 (22.9)	40 (38.1)	26 (24.8)	9 (8.6)	21 (20)
TIG + AMG	9 (8.6)	12 (11.4)	32 (30.5)	26 (24.8)	3 (2.9)	18 (17.1)
AMG + FOS	34 (32.4)	8 (7.6)	8 (7.6)	8 (7.6)	7 (6.7)	18 (17.1)
Triple combination therapy ($N = 72$, 63.2%)						
POL + TIG + CARB	12 (16.7)	39 (54.2)	36 (50)	22 (30.6)	21 (29.2)	40 (55.6)
POL + TIG + AMG	9 (12.5)	17 (23.6)	17 (23.6)	6 (8.3)	6 (8.3)	21 (29.2)
POL + TIG + FOS	4 (5.6)	14 (19.4)	8 (11.1)	6 (8.3)	8 (11.1)	13 (18.1)
POL + AMG + FOS	17 (23.6)	7 (9.7)	4 (5.6)	2 (2.8)	4 (5.6)	15 (20.8)
Double CARB + POL	8 (11.1)	11 (15.3)	7 (9.7)	5 (6.9)	12 (16.7)	13 (18.1)

L. Papst et al. / Clinical Microbiology and Infection 2018)

Monoterapiye kıyasla kombinasyonun üstünlüğü henüz tam olarak açıklanamamıştır.

Retrospektif çalışmalar, kombinasyon tedavisi ile daha düşük mortalite oranları olduğunu bildirmiştir. Ancak kanıt kalitesi düşük

Tumbarello, M Infections caused by KPC-producing Klebsiella pneumoniae: Dierences in therapy and mortality in a multicentre study. J. Antimicrob. Chemother. **2015**, 70, 2133–4213.
Tumbarello et al. Predictors of mortality in bloodstream infections caused by Klebsiella pneumonia carbapenemase producing K. pneumoniae: Importance of combination therapy. Clin. Infect. Dis. **2012**, 55,
Oren Zusman, Sergey Altun. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis J Antimicrob Chemother doi:10.1093/jac/dkw377

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

Summary

Background Colistin–carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria.

Lancet Infect Dis 2018
Published Online
February 15, 2018
http://dx.doi.org/10.1016/

- Yayınlanmış ilk prospektif RCT
- Kolistin monoterapi vs kolistin + meropenem
- Enterobacteriaceae hastaların % 18'i (73/406)
- Enterobacteriaceae infeksiyonlarının % 77'si KDİ ve K. pneumoniae (%89) majör patojen
- Enterobacteriaceae ile ilgili subgrup analizlerinde;
  - Klinik sonuçta fark yok
  - Klinik başarısızlık ve 28 gün mortalite kombinasyon grubunda daha az ama istatistiksel anlamlı değil....

	Colistin	Colistin and meropenem	Risk ratio (95% CI) for outcome with combination	p value
Per protocol population*				
n	169	185	..	..
Clinical failure	129 (76%)	131 (71%)	0·92 (0·82–1·05)	0·220
28-day mortality	69 (41%)	75 (41%)	0·97 (0·76–1·25)	0·840
14-day mortality	48 (28%)	53 (29%)	1·00 (0·72–1·39)	0·992
Inappropriate empirical antibiotic treatment†				
n	92	105	..	..
Clinical failure	74 (80%)	76 (72%)	0·91 (0·78–1·07)	0·254
28-day mortality	40 (43%)	44 (42%)	0·98 (0·71–1·36)	0·910
14-day mortality	34 (37%)	28 (27%)	0·74 (0·49–1·13)	0·166
Bloodstream infection, ventilator-associated pneumonia, or hospital-acquired pneumonia				
n	173	182	..	..
Clinical failure	141 (82%)	133 (73%)	0·9 (0·8–1·004)	0·059
28-day mortality	77 (45%)	81 (45%)	0·99 (0·79–1·25)	0·931
14-day mortality	55 (328%)	60 (33%)	1·04 (0·78–1·38)	0·804
Main pathogen				
n	198	208	..	..
Clinical failure				
Acinetobacter baumannii	125 (83%), n=151	130 (81%), n=161	0·97 (0·87–1·09)	0·643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0·78 (0·54–1·13)	0·185
Pseudomonas or others§	8 (62%), n=13	4 (50%), n=8	0·81 (0·36–1·84)	0·673
28-day mortality				
A baumannii	70 (46%), n=151	84 (52%), n=161	1·11 (0·87–1·41)	0·404
Enterobacteriaceae	12 (35%), n=34	8 (21%), n=39	0·62 (0·29–1·36)	0·235
Pseudomonas or others	4 (31), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0
14-day mortality				
A baumannii	54 (36%), n=151	62 (39%), n=161	1·11 (0·82–1·52)	0·495
Enterobacteriaceae	6 (18%), n=34	6 (15%), n=39	0·90 (0·32–2·51)	0·838
Pseudomonas or others	4 (31%), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0

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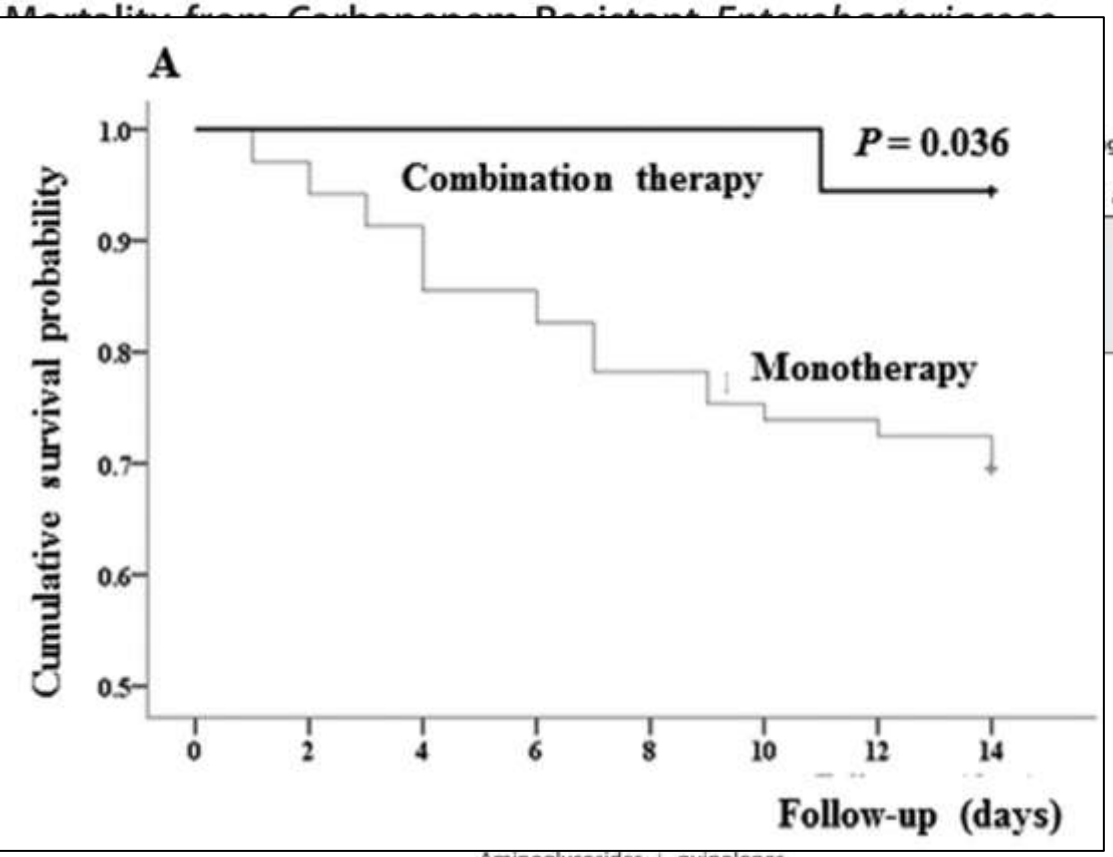
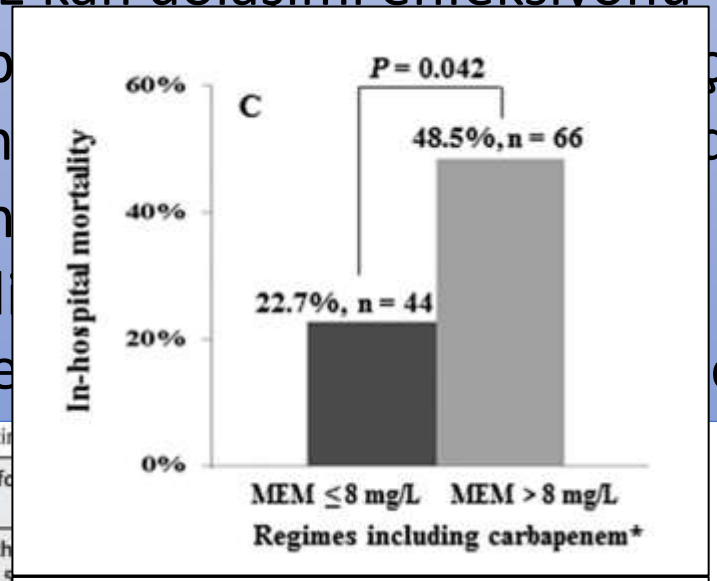
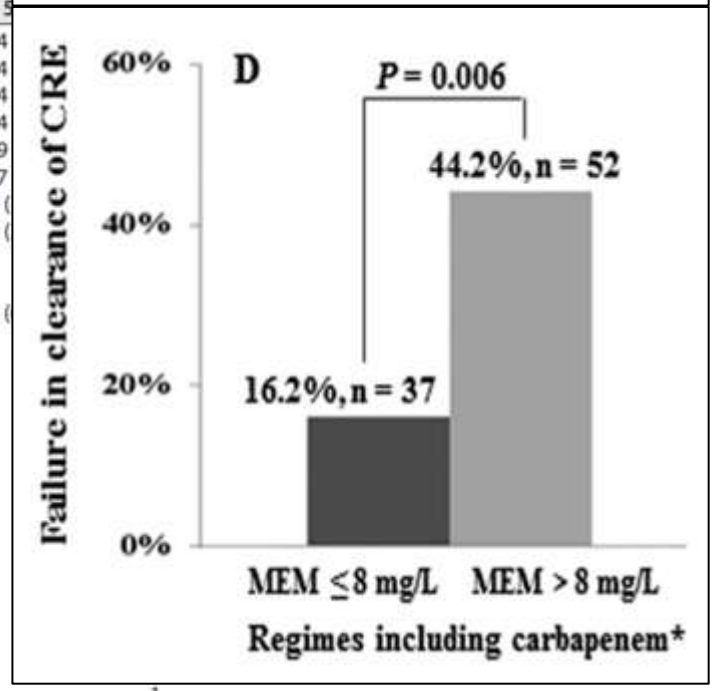
monote emiş.

Retrospective Observational Study from a Chinese Network of the Impact of Combination Therapy versus Monotherapy on







g Jin,[9]

active therapy based on *in vitro* anti

	No. of patients with the fo patients (%):		
	All patients (n = 164)	Death (n = 5	
	66/164 (40.2)	25/54	
	98/164 (59.8)	29/54	
	57/164 (34.8)	19/54	
	76/164 (46.3)	21/54	
	78/98 (79.6)	27/29	
	31/78 (39.7)	19/27	
	25/78 (32.1)	5/27 (	
	17/78 (21.8)	1/27 (	
	2	2	
	3	0	
	20/98 (20.4)	2/29 (	
	10/20 (50.0)	0	
	5	0	
	2	0	
	2	0	
	1	0	
	3	0	
	3	2	
Aminoglycosides + quinolones	1	0	
Aminoglycosides + fourth-generation cephalosporin	1	1	
Aminoglycosides + aztreonam + third-generation cephalosporin	1	1	
Including β-lactam–β-lactamases inhibitor	4	0	
β-Lactam–β-lactamases inhibitor + fourth-generation cephalosporin	1	0	
β-Lactam–β-lactamases inhibitor + aztreonam	1	0	
β-Lactam–β-lactamases inhibitor + minocycline	1	0	1
β-Lactam–β-lactamases inhibitor + quinolones	1	0	1

[a]Although polymyxin B is not available in China, two patients were treated with this drug, which was purchased from abroad.

January 2019 Volume 63 Issue 1 e01511-18
Antimicrobial Agents and Chemotherapy

J Antimicrob Chemother 2015; **70**: 2133–2143
doi:10.1093/jac/dkv086 Advance Access publication 21 April 2015

Journal of Antimicrobial Chemotherapy

Infections cau … in … erences

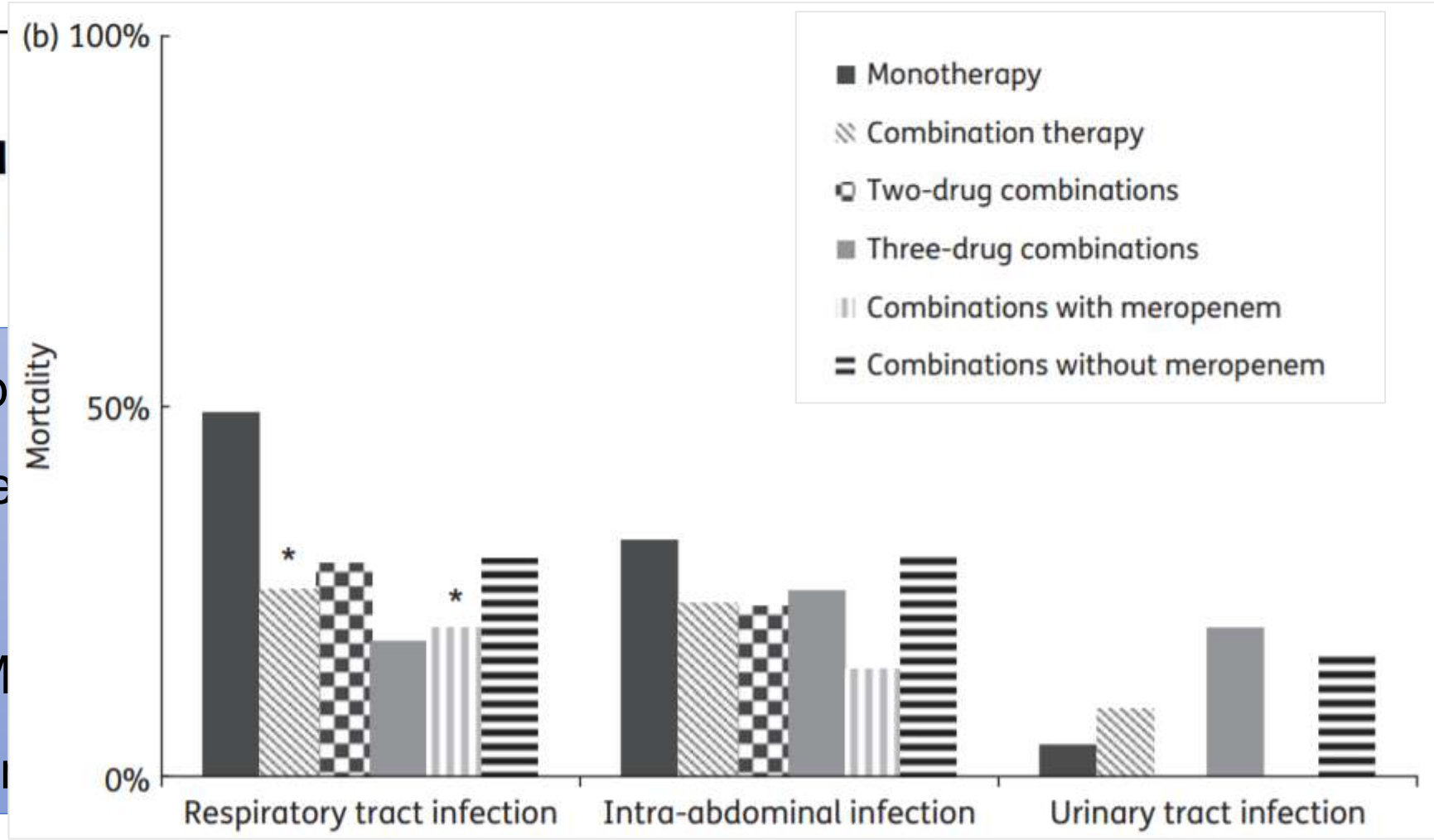
307 monoterap…

354 kombine te…

•İn vitro etkili 2…

•Meropenem M…

yüksek sağkalı…



Blood stream infections due to OXA-48-like carbapenemase-producing *Enterobacteriaceae*: treatment and survival

Ilker Inanç Balkan [a,*], Gökhan Aygün [b], Selda Aydın [a], Sibel Islak Mutcalı [a], Zehra Kara [c], Mert Kuşkucu [b], Kenan Midilli [b], Vicdan Şemen [b], Şükrü Aras [d], Mücahit Yemişen [a], Bilgül Mete [a], Reşat Özaras [a], Neşe Saltoğlu [a], Fehmi Tabak [a], Recep Öztürk [a]

[a] *Department of Infectious Diseases, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul 34098, Turkey*
[b] *Department of Clinical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey*
[c] *Department of Internal Medicine, Cerrahpaşa Medical Faculty, Istanbul University, Istanbul, Turkey*
[d] *Section of Biochemistry and Biostatistics, Ahenk Diagnostics, Istanbul, Turkey*

Treatment outcomes

	Total ($n=36$)	Survivors ($n=18$)	Non-survivors ($n=18$)	p-Value[a]
Time to active treatment, days, mean ± SD	1.25 ± 1.32	0.72 ± 1.18	1.78 ± 1.26	0.014
Duration of treatment, days, mean ± SD	14.58 ± 16.015	22.72 ± 18.68	6.44 ± 6.21	0.002[b]
Treatment modalities				
Colistin dual con				0.725
Colistin triple co				0.075
Non-colistin base				0.018
Carbapenem mo				1

[a] Univariate analy
[b] Duration of trea

OXA-48(+) Enterobacteriaceae

- 36 Kan Dolaşımı Enfeksiyonu, KDE
- 26 *K.pneumoniae, 12 E.Coli*
- 28.gün mortalitesi %50
- Kolistin içeren kombinasyonlarda mortalite daha az

MAYO CLINIC

TABLE 1. Characteristics of Patients With Bloodstream Infections Caused by Carbapenemase-Producing Enterobacteriaceae in the Derivation and Validation Cohorts[a,b]

Characteristic	Derivation cohort (n=314)	Validation cohort (n=154)	*P* value
Age (y)	65 (54-75)	69 (54.25-77)	.20[c]
Male sex	181 (57.6)	90 (58.4)	.87
Enterobacteriaceae			.65
Klebsiella pneumoniae	272 (86.6)	131 (85.1)	
Others	42 (13.4)	23 (14.9)	
Type of carbapenemase			.98
OXA	52 (16.6)	24 (15.6)	
KPC	234 (74.5)	117 (76.0)	
VIM	25 (8.0)	12 (7.8)	
Other metallo-β-lactamases	3 (1.0)	1 (0.6)	
Nosocomial acquisition	277 (89.6)	130 (87.2)	.45
Source of BSI			
Urinary or biliary tract	64 (20.7)	27 (18.1)	.51
Others	245[d] (79.3)	122[e] (81.9)	

INCREMENT Group

CrossMar

Fever (oral temperature)	
≤35°C or ≥40°C	2
35.1–36.0°C or 39.0–39.9°C	1
36.1–38.9°C	0
Hypotension	2
Acute hypotensive event with drop in systolic blood pressure > 30 mm Hg and diastolic blood pressure > 20 mm Hg or Requirement for intravenous vasopressor agents or Systolic blood pressure < 90 mm Hg	
Mechanical ventilation	2
Cardiac arrest	4
Mental status	
Alert	0
Disoriented	1
Stuporous	2
Comatose	4

Tablo I. Charlson Komorbidite İndeksi

Komorbidite	Ağırlıklı puan*
Miyokard infarktüsü; konjestif kalp yetmezliği; periferal vasküler hastalık; serebrovasküler hastalık; demans; kronik akciğer hastalığı; konnektif doku hastalığı; ülser; hafif karaciğer hastalığı; diabetes mellitus	1
Hemipleji; orta/ağır böbrek yetmezliği; diyabet (hedef organ hasarı +); neoplazi; lösemi/lenfoma	2
Orta veya ağır karaciğer hastalığı	3
Metastatik solid tümör; AIDS	6

* Toplam puan her bir komorbid durumun birbirine eklenmesiyle elde edilir. Kırk yaş üzerindeki her 10 yıl için bi puan eklenir (50-59: 1 puan, 60-69: 2 puan gibi).

INCREMENT CPE mortalite skoru	
Başlangıçta sepsis veya septik şok	5 puan
Pitt bakteremi skoru >6	4 puan
Charlson indeksi >2	3 puan
Bakteremi kaynağı üriner veya safra dışı	3 puan
Uygunsuz empirik tedavi	2 puan

INCREMENT CPE mortalite skoru	Mortalite oranı
0-8 düşük	18%
9-13 orta	50%
14-17 yüksek	80%

Gutierrez-Gutierrez B, et al. Mayo Clin Proc 2016;91:1362

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

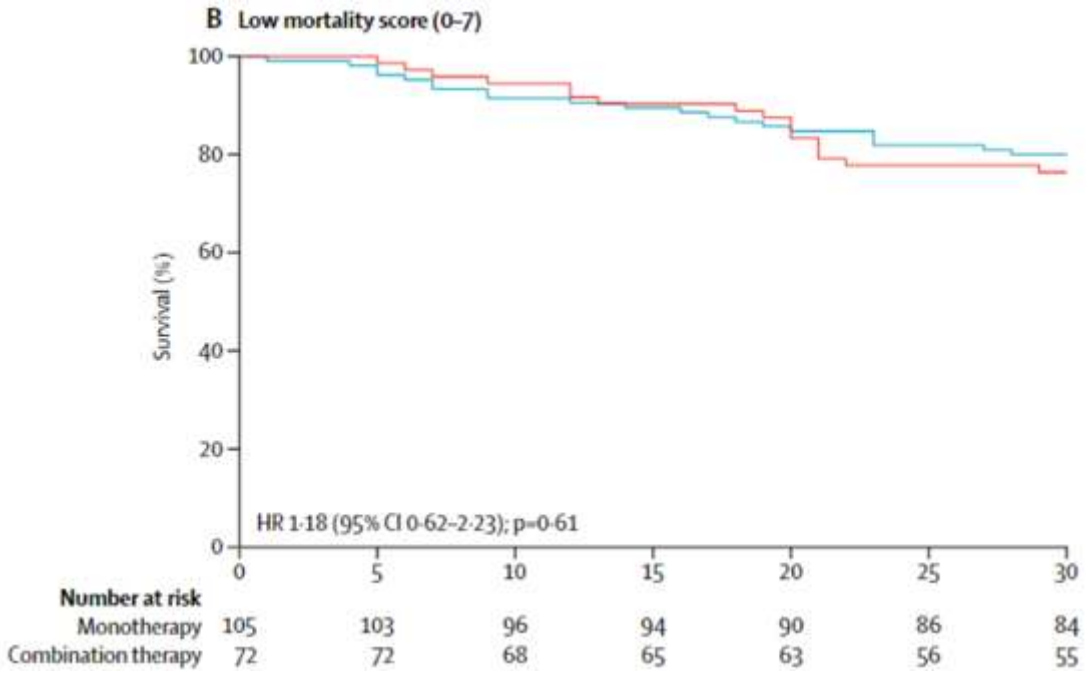
Belén Gutiérrez-Gutiérrez*, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†

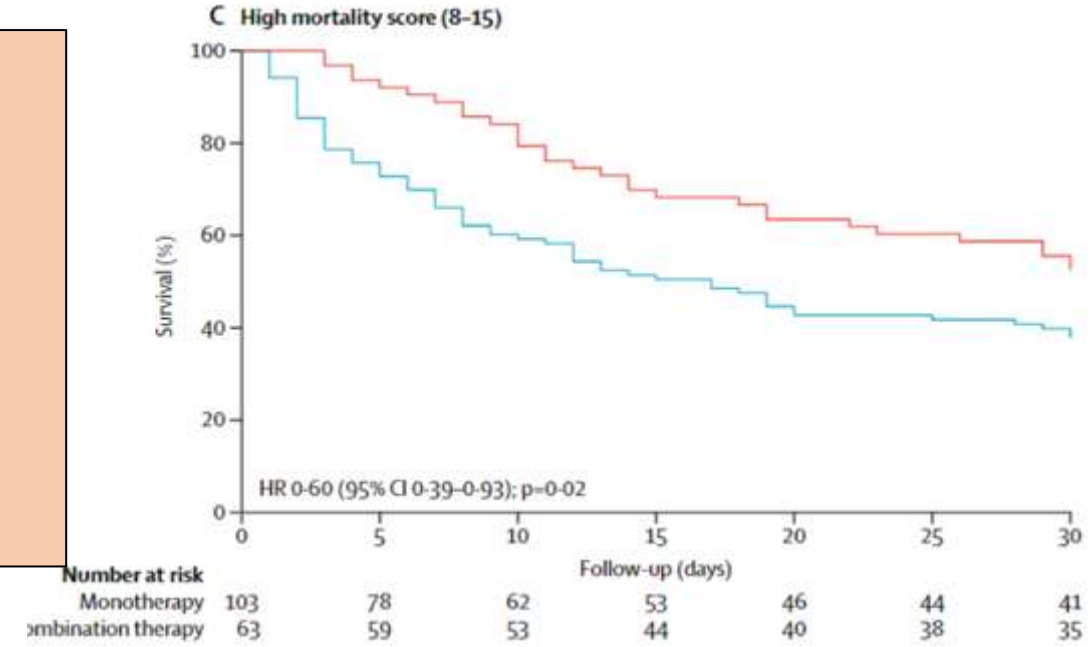
Lancet Infect Dis 2017; 17: 726–34
Published Online April 22, 2017
http://dx.doi.org/10.1016/S1473-3099(17)30228-1
See Comment page 677
*Contributed equally
†Investigators listed at end of paper

Summary

Background The best available treatment against carbapenemase-producing Enterobacteriaceae (CPE) is unknown. The objective of this study was to investigate the effect of appropriate therapy and of appropriate combination therapy on mortality of patients with bloodstream infections (BSIs) due to CPE.

Methods In this retrospective cohort study, we included patients with clinically significant monomicrobial BSIs due to CPE from the INCREMENT cohort, recruited from 26 tertiary hospitals in ten countries. Exclusion criteria were missing key data, death sooner than 24 h after the index date, therapy with an active antibiotic for at least 2 days when blood cultures were taken, and subsequent episodes in the same patient. We compared 30 day all-cause mortality between patients receiving appropriate (including an active drug against the blood isolate and started in the first 5 days





CP-Enterobacteriaceae'ye Bağlı Bakteremi Tedavisinde Kombinasyon Tedavisi

Uluslararası retrospektif kohort çalışması

– 11 üke, 26 hastane

– Sonlanım noktası 30 günlük mortalite

CP-CRE ile bakteremi gelişen 437 hasta

Kombinasyon tedavisi mortaliteyi ancak yüksek riskli hastalarda azaltıyor (skor 8-15)

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TABLE 3 Summary of recommended regimens for treatment of infections caused by carbapenem-resistant *Enterobacteriaceae*[a]

Risk level, therapy type, and isolate susceptibility	Drugs
High risk,[b] combination therapy	
Susceptible to a β-lactam (use according to susceptibility)	Backbone: ceftazidime-avibactam (preferred) or meropenem-vaborbactam; alternatively, meropenem (if MIC is ≤8 mg/liter) or ceftazidime or aztreonam Accompanying drug (no data available about the need for combination therapy if ceftazidime-avibactam or meropenem-vaborbactam is used as the backbone): colistin, tigecycline, aminoglycoside, or fosfomycin (if isolate is intermediate to the backbone drug, consider using 2 of these)
Resistant to all β-lactams (including isolates with meropenem MICs of >8 mg/liter), susceptible to at least 2 drugs, including colistin	Backbone: colistin Accompanying drug: tigecycline, aminoglycoside (high risk of nephrotoxicity), or fosfomycin
Resistant to all β-lactams and colistin, susceptible to at least 2 drugs	Backbone: tigecycline or aminoglycoside Accompanying drug: tigecycline or aminoglycoside, fosfomycin
Pandrug-resistant or susceptible to only one drug	Meropenem plus ertapenem or ceftazidime-avibactam plus aztreonam; add any active drug; consider active investigational drugs if available; consider *in vitro* testing of combinations for synergy
Low risk,[c] monotherapy	
According to susceptibility	Ceftazidime-avibactam, meropenem-vaborbactam, meropenem, ceftazidime, aztreonam, colistin, tigecycline, aminoglycoside (if intermediate susceptibility, choose another option or use combination)

Karbapenemlerin CRE enfeksiyonlarında kullanımı

- **Karbapenem MIC ≤ 8 (32??) mcg/mL ise kullanılabilir…**
- **Yüksek doz uzun süreli infüzyon uygulanmalıdır…**
  - **3x2 g/gün dozunda > 3 saat infüzyon!!!**
- **Eğer varsa, in vitro aktif başka bir ajanla kombine edilmelidir…**

Sheu CC et al. Frontiers in Microbiology 2019;10:80

Pathogenic kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD parameter	$fT_{>MIC}$	*f*Cmax/MIC	$fAUC_{0-24}$:MIC
Antimicrobials	β-lactams Lincosamide Erythromycin Clarithromycin Linezolid Flucytosine	Aminoglycosides Metronidazole Fluoroquinolones Daptomycin Echinocandins Polyenes	Fluoroquinolones Aminoglycosides Azithromycin Glycopeptides Tigecycline Linezolid Echinocandins Triazoles
Pathogenic kill target	>40% $fT_{>MIC}$ for carbapenems >50% $fT_{>MIC}$ for penicillin >70% $fT_{>MIC}$ for cephalosporins (Maximal pathogenic kill activity seen at 4–5xMIC for some agents)	$fCmax_{>8-10xMIC}$ (Maximal pathogenic kill activity is often seen when $fCmax_{>8-10xMIC}$)	Each antimicrobial is individualized (Dose is the main determinant of achieving maximal pharmacological efficacy.)

Tsai D, et al. Curr Opin Crit Care 2015;21:412

Continu
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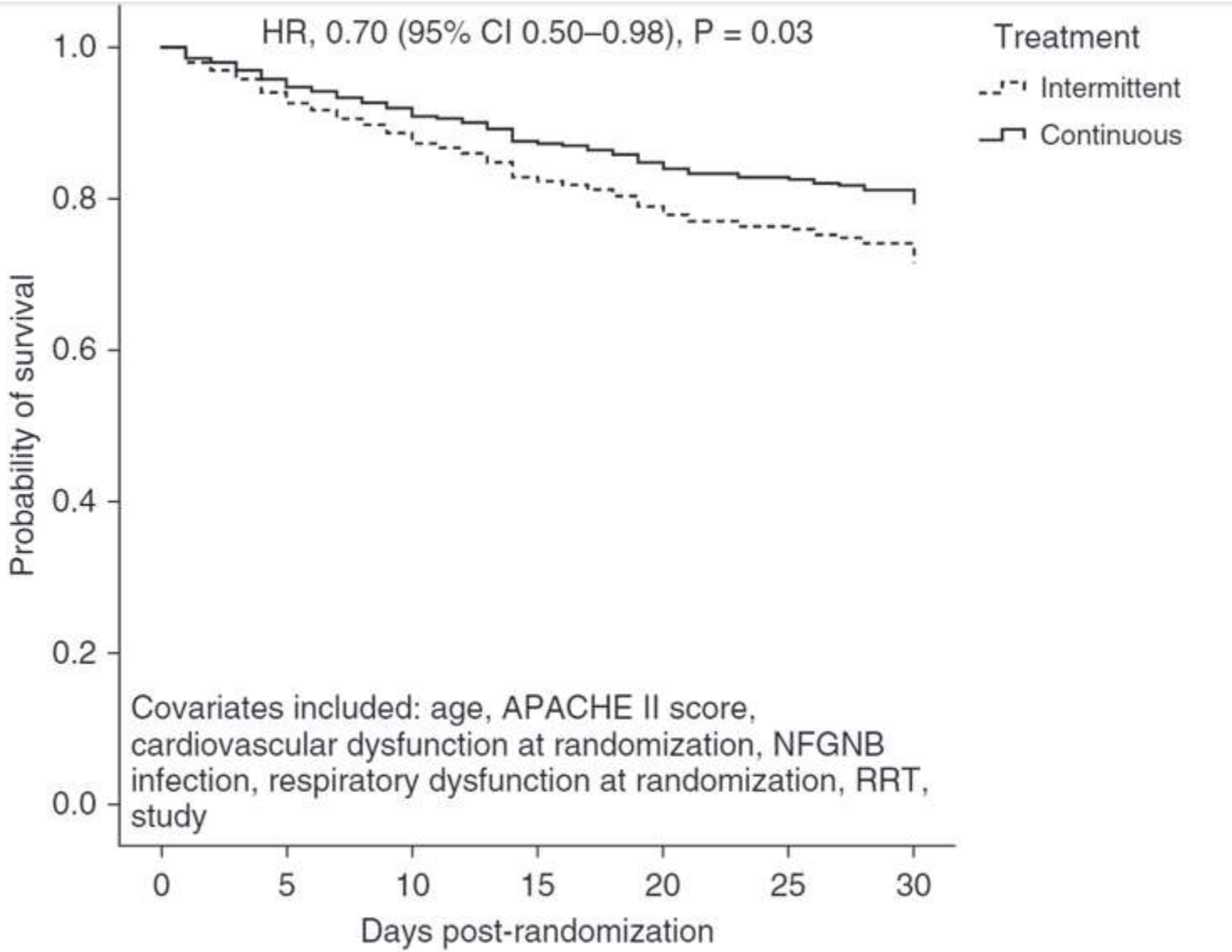

e Sepsis

O. Cotta[1,2,3,4],

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Health Research,
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Melbourne, Australia;

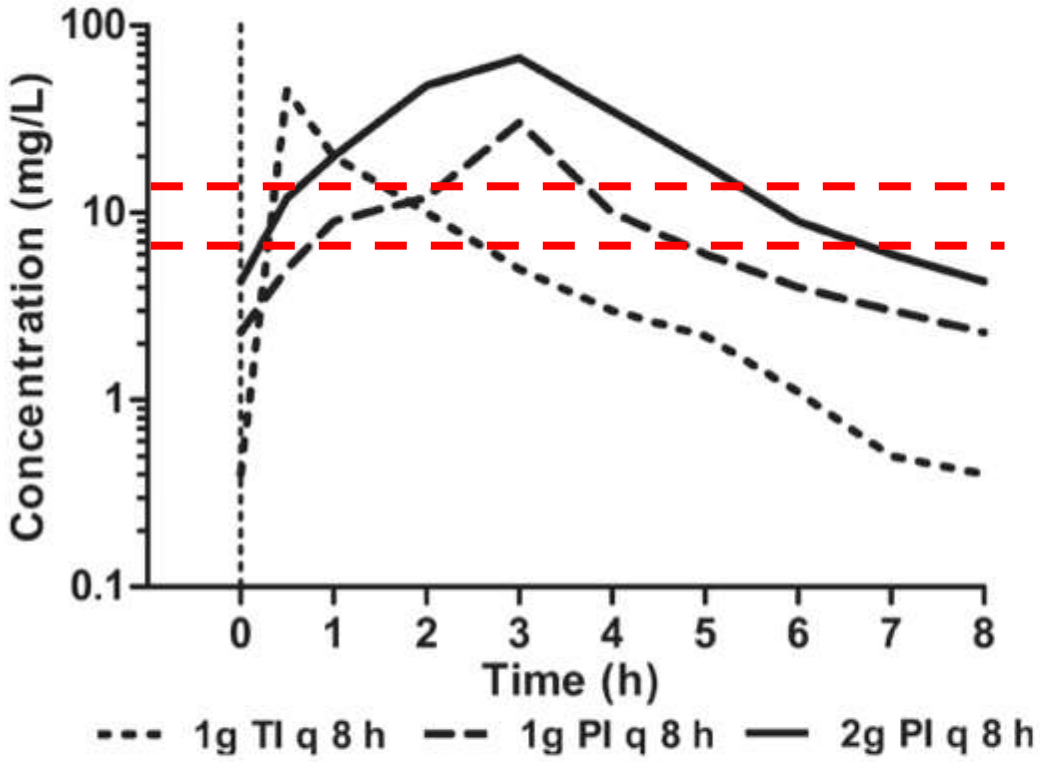

FIG. 1. Simulated concentration–time profiles of three different dosing regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [35,45,47].

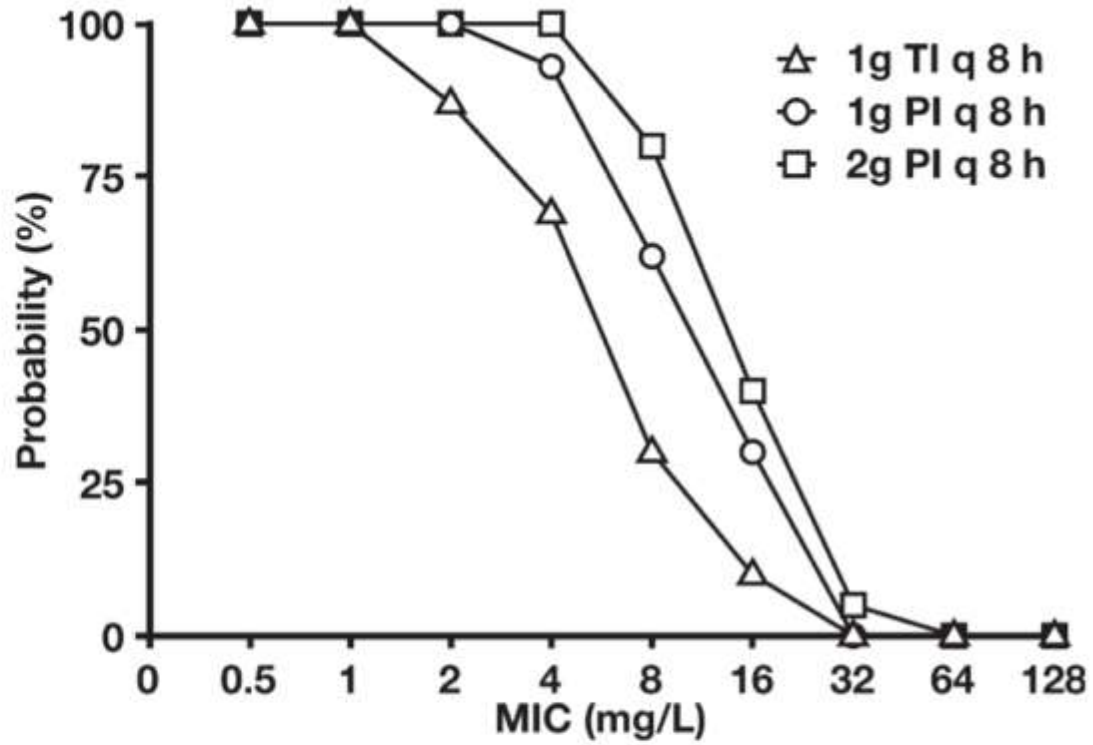

FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% *T* > MIC) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

- 1g TI q 8h ile 5 saat sonra EUCAST MIC sınır değer olan 2 mg/L'nin altına düşmekte..
- 1 g PI q 8H ile; dozlar arası sürenin tamamında 2mg/L'nin üzerinde olmakta…
- 2 g PI q 8H ile; konsantrasyon 4 mg/L'ye çıkmakta…

Farklı doz şemaları ile Monte-Carlo simulasyonu yapıldığında MIC 4 mg/L için %50T>MIC hedefine ulaşma olasılığı

- 1g TI q 8h ile % 69
- 1 g PI q 8H ile % 93
- 2 g PI q 8H ile; % 100

European Society of Clinical Microbiology and Infectious Diseases, CMI, 17, 1135–1141

Contents lists available at ScienceDirect

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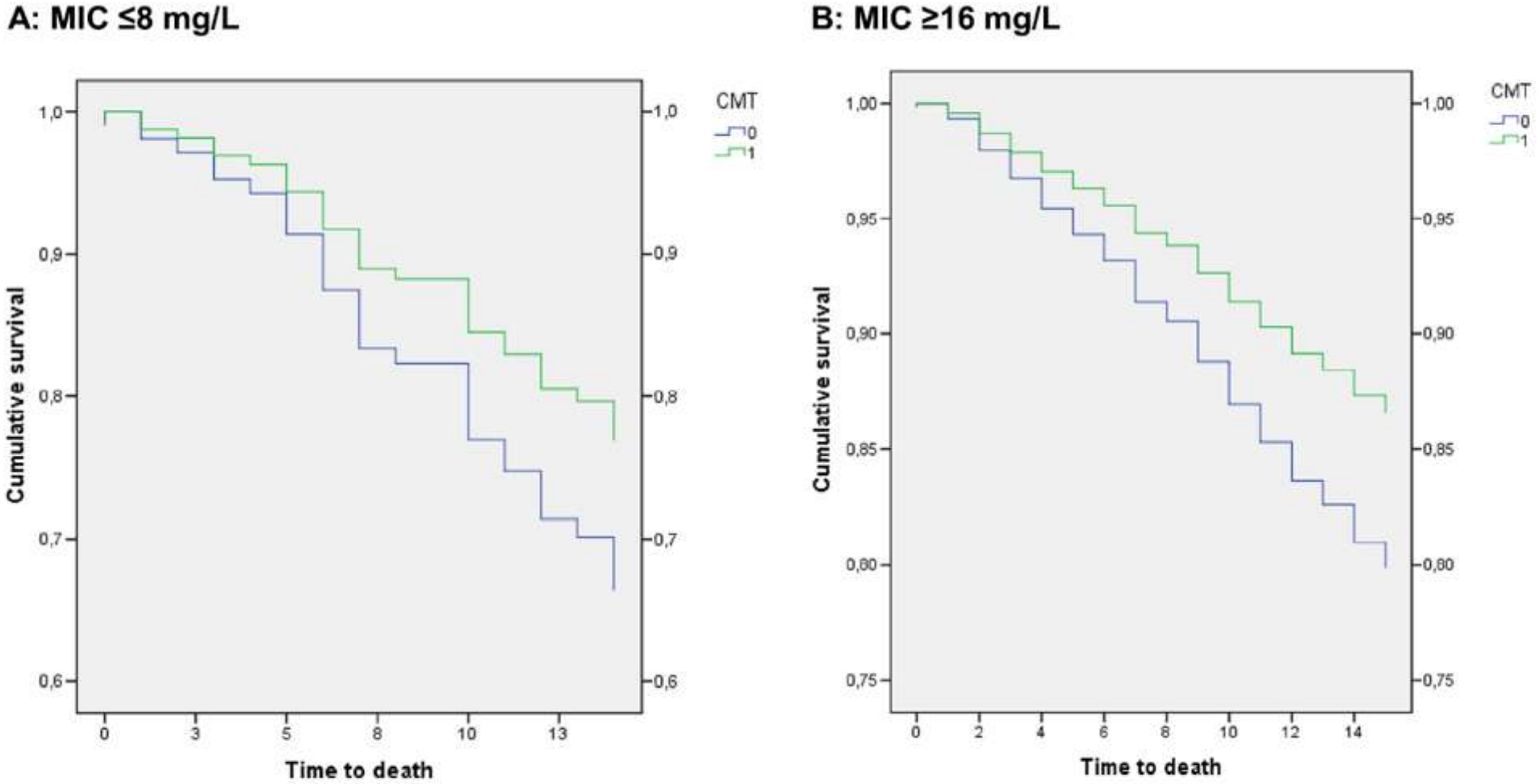

Fig. 1. Cox regression analysis of survival stratified for carbapenem MIC. **CMT:** combination with meropenem treatment: 0 no, 1 yes. Panel A and Panel B show cumulative survival at 14 days from CR-KP BSI onset for patients who did or did not receive carbapenem combination therapy, it was adjusted for all the covariates included in the Cox regression model and the propensity score. The model was further stratified according to the meropenem MIC ≤8 mg/L (Panel A), MIC ≥16 mg/L (Panel B), the overall aHR for the variable carbapenem combination therapy (CMT) was: 0.63, 95%CI 0.41–0.96, $P = 0.03$.

J Antimicrob Chemother 2016; **71**: 196–207
doi:10.1093/jac/dkv288 Advance Access publication 3 October 2015

Journal of Antimicrobial Chemotherapy

Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort

Mohd H. Abdul-Aziz[1], Jeffrey Lipman[1,2], Murat Akova[3], Matteo Bassetti[4], Jan J. De Waele[5], George Dimopoulos[6], Joel Dulhunty[1,2], Kirsi-Maija Kaukonen[7], Despoina Koulenti[1,6], Claude Martin[8,9], Philippe Montravers[10], Jordi Rello[11], Andrew Rhodes[12], Therese Starr[2], Steven C. Wallis[1] and Jason A. Roberts[1,2]* on behalf of the DALI Study Group†

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†All members of the DALI Study Group are listed in the Acknowledgements section.

Received 30 March 2015; returned 14 May 2015; revised 1 July 2015; accepted 17 August 2015

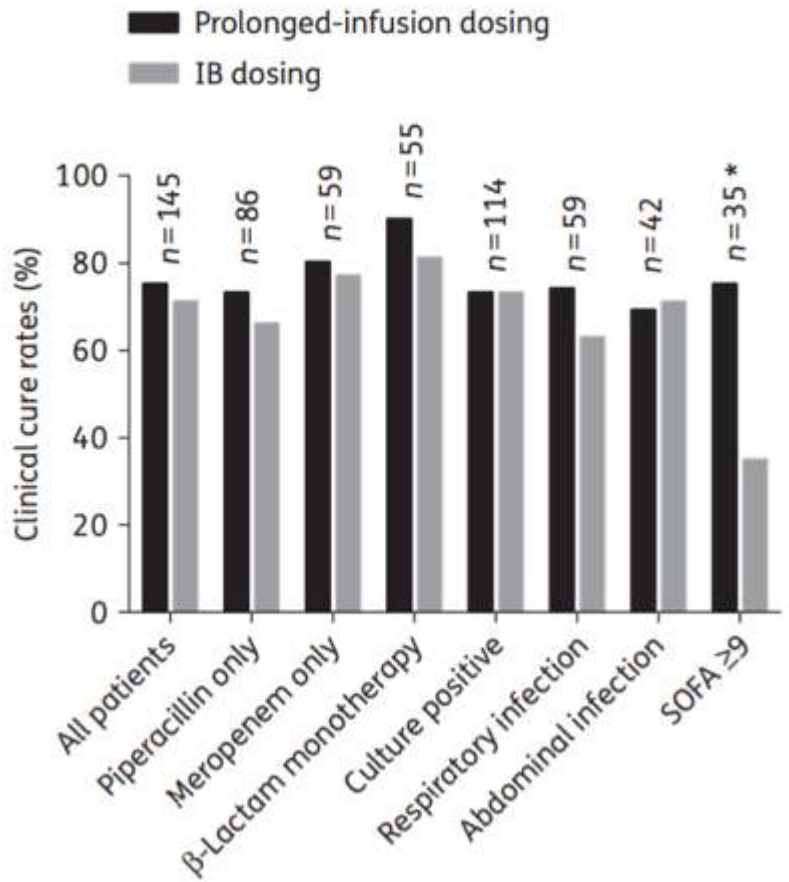
Objectives: We utilized the database of the Defining Antibiotic Levels in Intensive care unit patients (DALI) study to statistically compare the pharmacokinetic/pharmacodynamic and clinical outcomes between prolonged-infusion and intermittent-bolus dosing of piperacillin/tazobactam and meropenem in critically ill patients using inclusion criteria similar to those used in previous prospective studies.

Methods: This was a *post hoc* analysis of a prospective, multicentre pharmacokinetic point-prevalence study (DALI), which recruited a large cohort of critically ill patients from 68 ICUs across 10 countries.

Results: Of the 211 patients receiving piperacillin/tazobactam and meropenem in the DALI study, 182 met inclusion criteria. Overall, 89.0% (162/182) of patients achieved the most conservative target of 50% $fT_{>MIC}$ (time over which unbound or free drug concentration remains above the MIC). Decreasing creatinine clearance and the use of prolonged infusion significantly increased the PTA for most pharmacokinetic/pharmacodynamic targets. In the subgroup of patients who had respiratory infection, patients receiving β-lactams via prolonged infusion demonstrated significantly better 30 day survival when compared with intermittent-bolus patients [86.2% (25/29) versus 56.7% (17/30); $P=0.012$]. Additionally, in patients with a SOFA score of ≥9, administration by prolonged infusion compared with intermittent-bolus dosing demonstrated significantly better clinical cure [73.3% (11/15) versus 35.0% (7/20); $P=0.035$] and survival rates [73.3% (11/15) versus 25.0% (5/20); $P=0.025$].

Conclusions: Analysis of this large dataset has provided additional data on the niche benefits of administration of piperacillin/tazobactam and meropenem by prolonged infusion in critically ill patients, particularly for patients with respiratory infections.

- Pip/Tazo, Meropenem
- Uzamış infüzyon
- 115 hasta aralıklı, 67 hasta uzamış
- Solunum yolu enfeksiyonlarında mortalite daha az (p=0.012)
- SOFA 9 veya üzerinde olan hastalarda mortalite daha az(p=0.025)



Çift karbapenem tedavisi

- **Ertapenem yüksek afinitesi nedeniyle karbapenemaz türü hidrolitik enzimlere bağlanır (*Suisid İnhibitör Etki / «kurban molekül»)***
- **Diğer karbapenemin daha yüksek konsantrasyonlara ulaşarak bakterisidal aktivitesine izin verir..**
- **Bu kombinasyonun sinerjistik etkisi, yüksek karbapenem direncinde bile gözlenmiş…**
- **Ancak çalışmalar KPC karbapenemazlarda yoğunlaşmış, diğer genotiplerle ilgili ileri çalışmalara ihtiyaç var…**

Çift karbapenem tedavisi

Ertapenem 1 g
30-60 dakika
infüzyon

1 saat sonra

Meropenem 3x2 g
> 3 saat infüzyon

Mashni O et al. Annals of Pharmacotherapy 2018;1–12

Critical Review of Double-Carbapenem Therapy for the Treatment of

Annals of Pharmacotherapy
1–12

DOI: 10.1177/1060028018790573

Table 2. (continued)

	Reference					
	De Pascale et al,[29] 2017	Venugopalan et al,[30] 2017	Oliva et al,[31] 2017	Souli et al,[32] 2017	Cprek and Gallagher,[33] 2015	Oliva et al,[34] 2016
Type of infection,[d] n (%)						
Bacteremia	37 (77.1%)	9 (50%)	18 (56.3%)	13 (48.1%)	7 (38.9%)	5 (33.3%)
Pneumonia	25 (52.1%)	3 (16.7%)	9 (28.1%)	1 (3.7%)	5 (27.8%)	1 (6.7%)
Urinary tract	3 (6.3%)	6 (33.3%)	9 (28.1%)	12 (44.4%)	3 (16.7%)	8 (53.3%)
Intra-abdominal	9 (18.8%)	0 (0)	0 (0)	0 (0)	2 (11.1%)	0 (0)
Others	1 (2.1%)	1 (5.6%)	9 (28.1%)	1 (3.7%)	1 (5.6%)	4 (26.7%)
Multiple sites	4 (8.3%)					2 (13.3%)
Sepsis/septic shock, n (%)	• Sepsis: NR • Septic shock: 36 (75%)	NR	• Sepsis: 18 (56.3%) • Septic shock: 8 (25%)	• Sepsis: 21 (77.8%) • Septic shock: 6 (22.2%)	NR	• Sepsis: 7 (46.7%) • Septic shock: 1 (6.7%)
Type of carbapenemase enzyme	• Class A carbapenemase (>90%) • Class B metallo-β-lactamase (<10%) • Class D carbapenemase (<10%)	NR	NR	KPC-2	NR	KPC-3
Outcomes						
Clinical success/cure, n (%)	30 (62.5%)	13 (72.2%)	24 (75%)	21 (77.8%)	7 (38.9%)	12 (80%)
Microbiological success, n (%)	22 (50%), Analyzed in 44 patients	15 (93.8%), Analyzed in 16 patients	NR	20 (74.1%)	11 (78.6%), Analyzed in 14 patients	12 (80%)
Adverse events related to DCT, n (%)	None reported	Seizure, 1 (5.5%)	• Seizure, 2 (6.3%) • Sodium disorder, 1 (3.1%) • Vomiting, 1 (3.1%) • Leukopenia, 2 (6.3%)	• Rash, 1 (3.7%) • Eosinophilia, 1 (3.7%) Meningitis, 2 (7.4 %)	Seizure, 2 (11.1%)	• Seizure, 1 (6.7%) • Nausea, 1 (6.7%) • Hypernatremia, 1 (6.7%)
Mortality (%)	28-Day mortality: 29.2%	30-Day mortality: 31.3%	60-Day mortality: 18.8%	Crude mortality: 29.6%	30-Day mortality: 27.8%	60-Day mortality: 6.7%

RESEARCH Open Access

Double carbapenem as a rescue strategy for the treatment of severe carbapenemase-producing *Klebsiella pneumo* matched

Gennaro De Pascal
Daniele Di Carlo[3], V
Piera Polidori[4], Tere

Combined targeted therapy
- DC + colistin
- DC + gentamicin
- DC + tigecycline

Değişken	ÇK grubu (n=48) (%)	Standart tedavi grubu (n=96) (%9	*p*
28 günlük mortalite	**14 (29.2)**	**46 (47.9)**	**0.04**
90 günlük mortalite	24 (50)	58 (60.4)	0.31
Klinik kür	30 (62.5)	47 (48.9)	0.17
Mikrobiyolojik eradikasyon	22 (50)	31 (38.3)	0.27
İnfeksiyon sonrası MV süresi	14 (7.5-31)	11.5 (7-19)	0.16
İnfeksiyon sonrası vazopressör süresi	10.5 (3.5-27.5)	8 (4.5-12)	0.19

- Olg
- 48/
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  - P
  - Sekonder sonlanım: Klinik kür, mikrobiyolojik erdikasyon, vazopressör ve MV süresi, 90 günde mortalite

Fosfomisin

- Güvenlik ve iyi tolere ediliyor
- Dağılım hacmi geniş.
- Monoterapi direnç gelişebilir.
- 4g/6h (toplam 24 grama kadar çıkılabilir)
- Karbapenemaz üreten *Klebsiella* için imipenem, meropenem, kolistin, netilmisin veya tigesiklin kombinasyonu %30-74 sinerjik

Reffert JL et al. Pharmacother 2014

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136 KPC üreten *K. pneumoniae* izolatı test edilmiş

Short Communication

In vitro antibacterial activity of fosfomycin combined with other antimicrobials against KPC-producing *Klebsiella pneumoniae*

Wei Yu [a], Ping Shen [a], Zhang Bao [b], Kai Zhou [a], Beiwen Zheng [a], Jinru Li [a], Lihua Guo [a],

Table 1
Multilocus sequence typing (MLST), minimum inhibitory concentrations (MICs) and fractional inhibitory concentration indices (FICIs) of fosfomycin (FM), tigecycline (TGC), imipenem (IMP), ertapenem ERT), colistin (COL) and amikacin (AMK) against four KPC-producing *Klebsiella pneumoniae* strains in time–kill assays.

Strain	MLST	MIC (mg/L)						FICI				
		FM	IMP	ETP	TGC	COL	AMK	FM + IMP	FM + ETP	FM + TGC	FM + COL	FM + AMK
ATCC BAA-1705	ST258	1	4	8	2	0.5	64	0.5	0.62	1.25	0.5	0.62
18253	ST11	16	16	256	2	>32	4	0.75	0.75	1	2	0.5
17186	ST11	8	16	128	1	0.25	1	0.75	0.75	0.56	0.5	0.62
17368	ST11	16	16	256	1	0.5	2	0.75	0.75	0.62	0.5	0.62

Table 2
Fractional inhibitory concentration indices (FICIs) of fosfomycin (FM) combined with other agents against 136 KPC-producing *Klebsiella pneumoniae* isolates.

FM plus	Synergistic (FICI ≤ 0.5)			Additive (0.5 < FICI ≤ 1)			Indifferent (1 < FICI ≤ 2)			Antagonistic (FICI > 2)		
	Total [*n* (%)]	FM-S (%)	FM-R (%)	Total [*n* (%)]	FM-S (%)	FM-R (%)	Total [*n* (%)]	FM-S (%)	FM-R (%)	Total [*n* (%)]	FM-S (%)	FM-R (%)
IMP	21 (15.4%)	20.7	11.5	114 (83.8%)	77.6	88.5	1 (0.7%)	1.7	0	0	0	0
ETP	30 (22.1%)	34.5	12.8	104 (76.5%)	62.0	87.2	2 (1.5%)	3.5	0	0	0	0
TGC	2 (1.5%)	1.7	1.3	113 (83.1%)	74.1	89.7	19 (14.0%)	24.2	6.4	2 (1.5%)	0	2.6
COL	5 (3.7%)	3.5	3.9	109 (80.1%)	79.3	80.8	22 (16.2%)	17.2	15.3	0	0	0
AMK	7 (5.1%)	5.2	5.1	109 (80.1%)	87.9	74.4	20 (14.7%)	6.9	20.5	0	0	0

IMP, imipenem; ETP, ertapenem; TGC, tigecycline; COL, colistin; AMK, amikacin; S, susceptible; R, resistant.

Fosfomisin, imipenem-ertapenem-tigesiklin-kolistin ve amikasin'in antibakteriyel etkinliğini artırmış
Özellikle fosfomisin-amikasin en etkin kombinasyon olarak saptanmış

Kolistin-Fosfomisin

- Karbapenemaz sentezleyen *Klebsiella pneumoniae* suşlarında, fosfomisin-kolistin kombinasyonunun bakterisidal etkiyi artırdığı, ancak kolistin dirençli olan izolatlarda bu etkinin olmadığı görülmüştür.

- Kolistin dirençli izolatlarda bakterisidal etkinin artırılması için fosfomisin konsantrasyonunun artırılması gerektiği vurgulanmaktadır.

Wang J, He JT, Bai Y, Wang R, Cai Y. Synergistic activity of colistin/fosfomycin combination against carbapenemase- producing Klebsiella pneumoniae in an in vitro pharmacokinetic/ pharmacodynamic model. Biomed Res Int 2018;2018:5720417.

26. Zhao M, Bulman ZP, Lenhard JR, Satlin MJ, Kreiswirth BN, Walsh TJ, et al. Pharmacodynamics of colistin and fosfomycine: a "treasure trove" combination combats KPC-producing Klebsiella pneumoniae. J Antimicrob Chemother 2017;72:1985-90.

27. Souli M, Galani I, Boukovalas S, Gourgoulis MG, Chryssouli Z, Kanellakopoulou K, et al. In vitro interactions of antimicrobial combinations with fosfomycine against KPC-producing Klebsiella pneumoniae and protection of resistance development. Antimicrob Agents Chemother 2011;55:2395-7.

Tigesiklin

- 100 mg yükleme dozu, ardından her 12 saatte bir 50 mg; Ancak geniş dağılım hacmi ve dokularda konsantre olması nedeniyle KDİ'larında etkinliği şüpheli

- Yükleme dozu 200 mg, ardından her 12 saatte bir 100 mg

SheuCC et al. Frontiersin Microbiology2019;10:80

Medicine
SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

Wentao Ni, MD, Yuliang Han, MD, Jie Liu, MD, Chuanqi Wei, MD, Jin Zhao, MD, Junchang Cui, MD, Rui Wang, PhD, and Youning Liu, MD

Tigesiklinin CRE enfeksiyonlarındaki etkinliğini değerlendiren 26 çalışma

Subgrup analizlerinde yüksek doz tigesiklin ile daha düşük YBÜ mortalitesi (OR= 12.48)

TABLE 4. Subgroup Analysis of Mortality Using Different Tigecycline Regimens to Treat Carbapenem-Producing *Enterobacteriaceae* and Carbapenem-Resistant *Enterobacteriaceae* Infections

Variables	Mortality Type	Studies, No. (Patients, No.)	Mortality Difference OR (95% CI); *P*	Heterogeneity of Studies Included
Monotherapy vs combination	30-day	9 (317)	1.83 (1.07–3.12); $P=0.03$	$I^2=0\%$; $Q=7.81$; $P=0.45$
	Infection-related	3 (59)	1.75 (0.33–9.27); $P=0.51$	$I^2=46.34\%$; $Q=3.73$; $P=0.16$
	14-day	2 (42)	1.00 (0.34–2.99); $P=1.00$	$I^2=0\%$; $Q=0.65$; $P=0.42$
	ICU	2 (62)	1.10 (0.11–10.67); $P=0.94$	$I^2=46.29\%$; $Q=1.86$; $P=0.17$
Double combination* vs triple combination†	30-day	8 (205)	2.18 (1.03–4.63); $P=0.04$	$I^2=4.31\%$; $Q=6.27$; $P=0.39$
	Infection-related	4 (58)	0.63 (0.16–2.54); $P=0.51$	$I^2=0\%$; $Q=1.05$; $P=0.59$
High dose vs standard dose‡	30-day	2 (47)	2.25 (0.55–9.24); $P=0.26$	$I^2=0\%$; $Q=0.02$; $P=0.90$
	ICU	2 (62)	12.48 (2.06–75.43); $P=0.006$	$I^2=0\%$; $Q=0.22$; $P=0.64$

Seftazidime-Avibaktam

- Şubat 2015'de onaylanmıştır.
- **Komplike intraabdominal infeksiyonlar**da
- Pyelonefriti de kapsayan **komplike üriner sistem** infeksiyonları
- Hastane kaynaklı **pnömoni** ve **VİP**

Shirley M. Drugs 2018;78:675-92.

Seftazidime-Avibaktam

- *Enterobacteriaceae ü*yeleri ve *P. aeruginosa*
- Avibaktam **GSBL** (TEM, SHV), **Amp C**, ile **sınıf A (**KPC, IMI vb.) ve **sınıf D** (OXA) **karbapenemazlara** etkili
- **Sınıf B**'deki **Metallo-betalaktamazlar** (NDM,IMP,VIM) **ETKİSİZ**
- *Acinetobacter*, Gram (+) ve anaeroplara karşı minimal etkinlik

Shirley M. Drugs 2018;78:675-92.

Seftazidime-Avibaktam

Clinical Infectious Diseases

BRIEF REPORT

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Ryan K. Shields,[1,2,a] Brian A. Potoski,[1,2,3,a] Ghady Haidar,[1] Binghua Hao,[4] Yohei Doi,[1] Liang Chen,[5] Ellen G. Press,[1] Barry N. Kreiswirth,[6] Cornelius J. Clancy,[1,4,5] and M. Hong Nguyen[1,2,4]

Thirty-seven carbapenem-resistant Enterobacteriaceae (CRE)-infected patients were treated with ceftazidime-avibactam. Clinical success and survival rates at 30 days were 59% (22/37) and 76% (28/37), respectively. In 23% (5/22) of clinical successes, CRE infections recurred within 90 days. Microbiologic failure rate was 27% (10/37). Ceftazidime-avibactam resistance was detected in 30% (3/10) of microbiologic failures.

Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature

Ryan K. Shields,[1,2] M. Hong Nguyen,[1,2] Ellen G. Press,[1] Liang Chen,[3] Barry N. Kreiswirth,[3] and Cornelius J. Clancy[1,2,4]

Mikrobiyolojik başarısızlık saptananların % 30'unda (3/10) CAZ-AVI direnci.....

CAZ-AVI ile 10-19 gün tedavi sonrası «*bla* rmKPC-3» genindeki mutasyonlara bağlı direnç!!

Shields RK et al. CID 2016;63(12):1615–8
Shields RK et al. Open Forum Infect Dis 2017

Meropenem-vaborbaktam

- Ağustos 2017'de komplike üriner sistem enfeksiyonlar **(cUTI)** için FDA onayı…
- **Vaborbaktam**

  Ambler **sınıf A** β-laktamazlar; (GEM, SHV, CTX-M ve **KPC**)

  Ambler **sınıf C** β-laktamazlar(AmpC) de **ETKİLİ….**

  Ambler**sınıf BMBLs(IMP, VIM, NDM)** ve **sınıf D**(**OXA-48**) β-laktamazlara **ETKİLİ DEĞİL…**

Shirley M. Drugs 2018;78:675-92.

Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations

Jason M Pogue ✉, Robert A Bonomo, Keith S Kaye

Clinical Infectious Diseases, Volume 68, Issue 3, 1 February 2019, Pages 519–524,
https://doi.org/10.1093/cid/ciy576

Table 1: In vitro activity of ceftazidime/avibactam and meropenem/vaborbactam against problematic Gram-negative pathogens

Organism	Resistance present	Ceftazidime/avibactam	Meropenem/vaborbactam
Enterobacteriaceae			
	ESBL	+++	+++
	AmpC	+++	+++
	KPC	+++	+++
	MBL	-	*
	OXA-48 like	+++	*

Plazomisin

- Temmuz 2018'de komplike üriner sistem enfeksiyonları **(cUTI)** için FDA onayı…
- İn vitro çalışmalarda meropenem ve/veya tigesiklin ile kombinasyonunda CRE izolatlarında artmış etkinlik….

SheuCC et al. Frontiersin Microbiology2019; 10.80

Eravasiklin

- Tetrasiklin sınıfından sentetik «fluorocyclin» antibiyotik…
- Ağustos 2018'de komplike intra abdominal infeksiyonlar(cIAI) için FDA onayı…
- In-vitro çalışmalarda CRE'ye karşı tigesiklinden 2 kat etkili!!!

SheuCC et al. Frontiersin Microbiology2019; 10.80

Sonuç

Gram-negatif enterik bakterilerde direnç giderek artmakta…

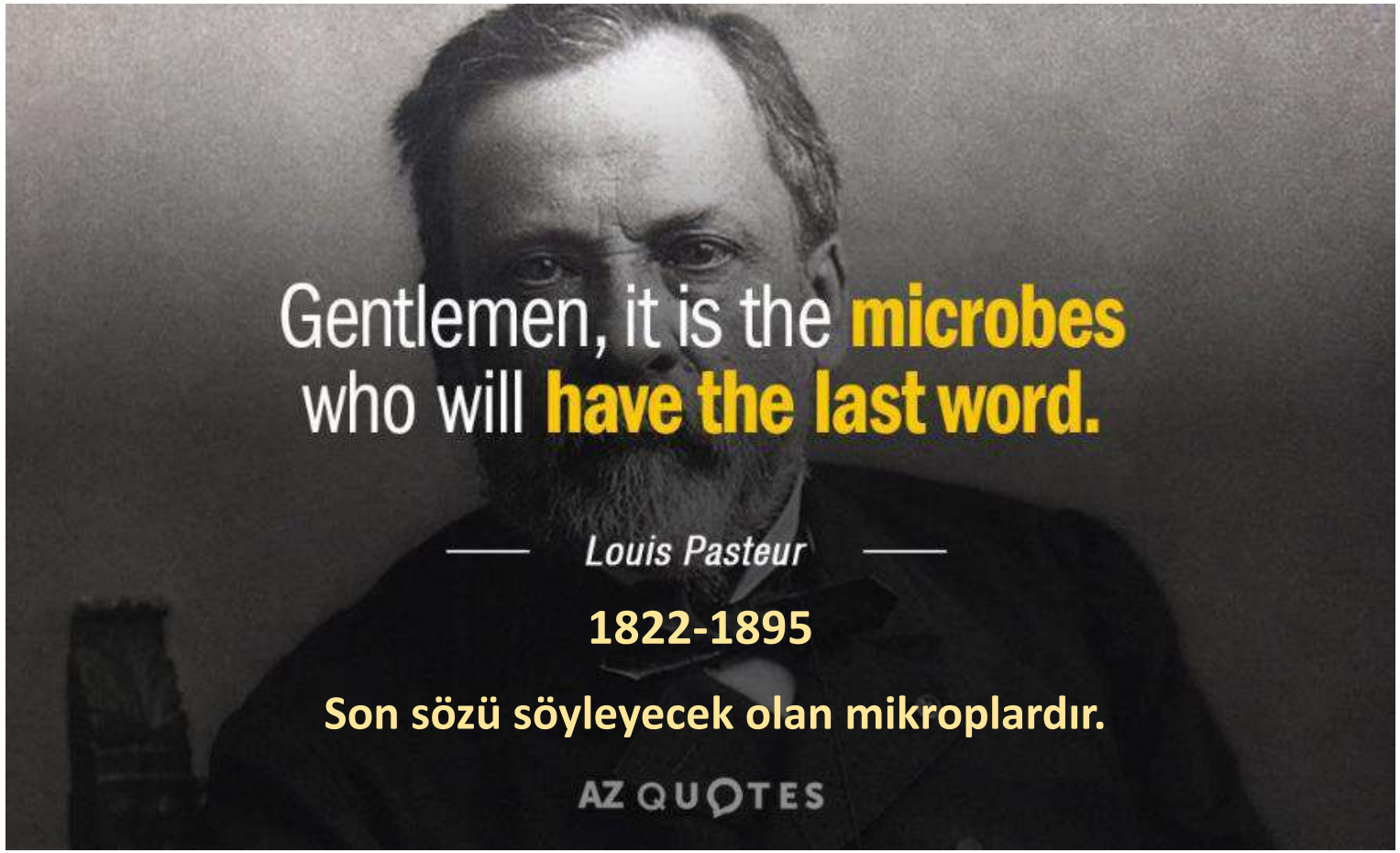
ESBL (+) patojenlerle meydana gelen enfeksiyonlarda karbapenemler hala ilk seçenek…

CRE enfeksiyonlarında kolistin, tigesiklin, aminoglikozidler in vitro duyarlılık testlerine göre kullanılabilecek ajanlar…

Kombinasyon tedavisi ağır hastalarda daha başarılı!!!

Karbapenemler MIC değerlerine göre hala bir seçenek: Ama yüksek doz ve uzamış infüzyon uygulanmalı + çift karbapenem tedavisi de uygun olabilecek bir diğer alternatif…

Yeni antibiyotikler umut vadediyor, ancak OXA-48 etkinlikleri < KPC!!!



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