Kolistin
Direnç Mekanizmaları
Risk Faktörleri, Tedavi

Dr. Gül Ruhsar YILMAZ

Süleyman Demirel Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

Etki Mekanizması

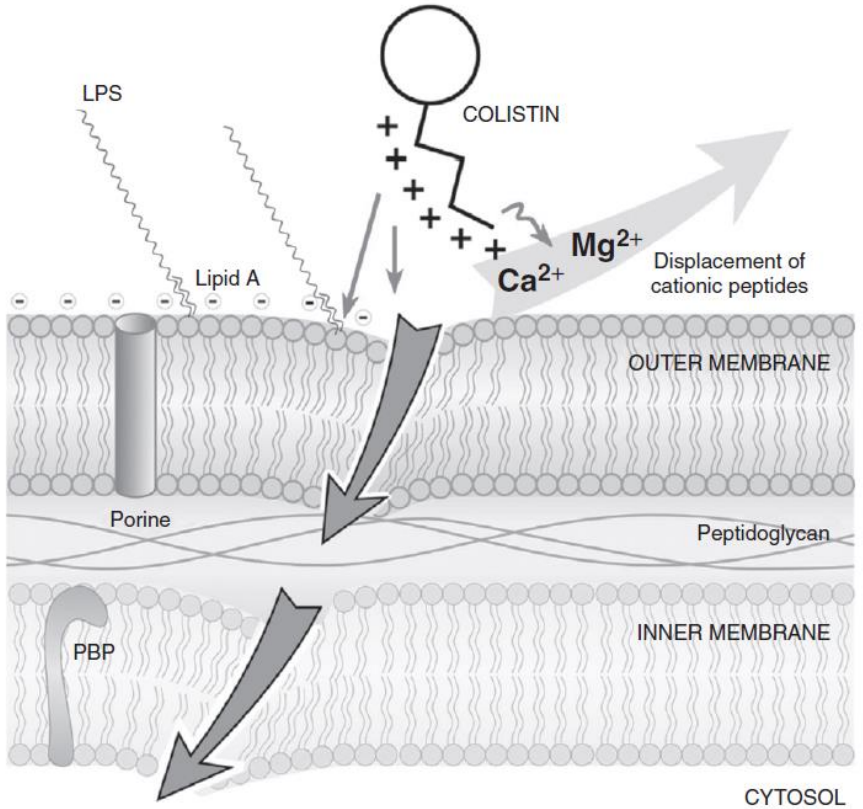


Figure 3. Action of colistin on bacterial membrane. The cationic cyclic decapeptide structure of colistin binds with the anionic LPS molecules by displacing calcium and magnesium from the outer cell membrane of Gram-negative bacteria, leading to permeability changes in the cell envelope and leakage of cell contents. By binding to the lipid A portion of LPS, colistin also has an anti-endotoxin activity. Disruption of the membranes should promote permeability for more conventional anti-pseudomonals. LPS: lipopolysaccharides; PBP: penicillin-binding protein. (From Martis *et al.*[58]).

Current Medical Research and Opinion 2015;31:707-721

Direnç

- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*

MDR
XDR
PDR

Current Medical Research and Opinion 2015;31:707-721

Table 1
Colistin and polymyxin B interpretative breakpoints in (μg/mL) recommended by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines in 2017.

Organism	Polymyxin	CLSI			EUCAST		
		S	I	R	S	I	R
Enterobacteriaceae	Colistin	–	–	–	≤2	–	>2
	Polymyxin B	–	–	–	–	–	–
Pseudomonas spp.	Colistin	≤2	–	≥4	≤2	–	>2
	Polymyxin B	≤2	4	≥8	–	–	–
Acinetobacter spp.	Colistin	≤2	–	≥4	≤2		>2
	Polymyxin B	≤2	–	≥4	–	–	–

S, susceptible; I, intermediate; R, resistant.

J of Global Antimicrob Resistance 2018;12:124-36

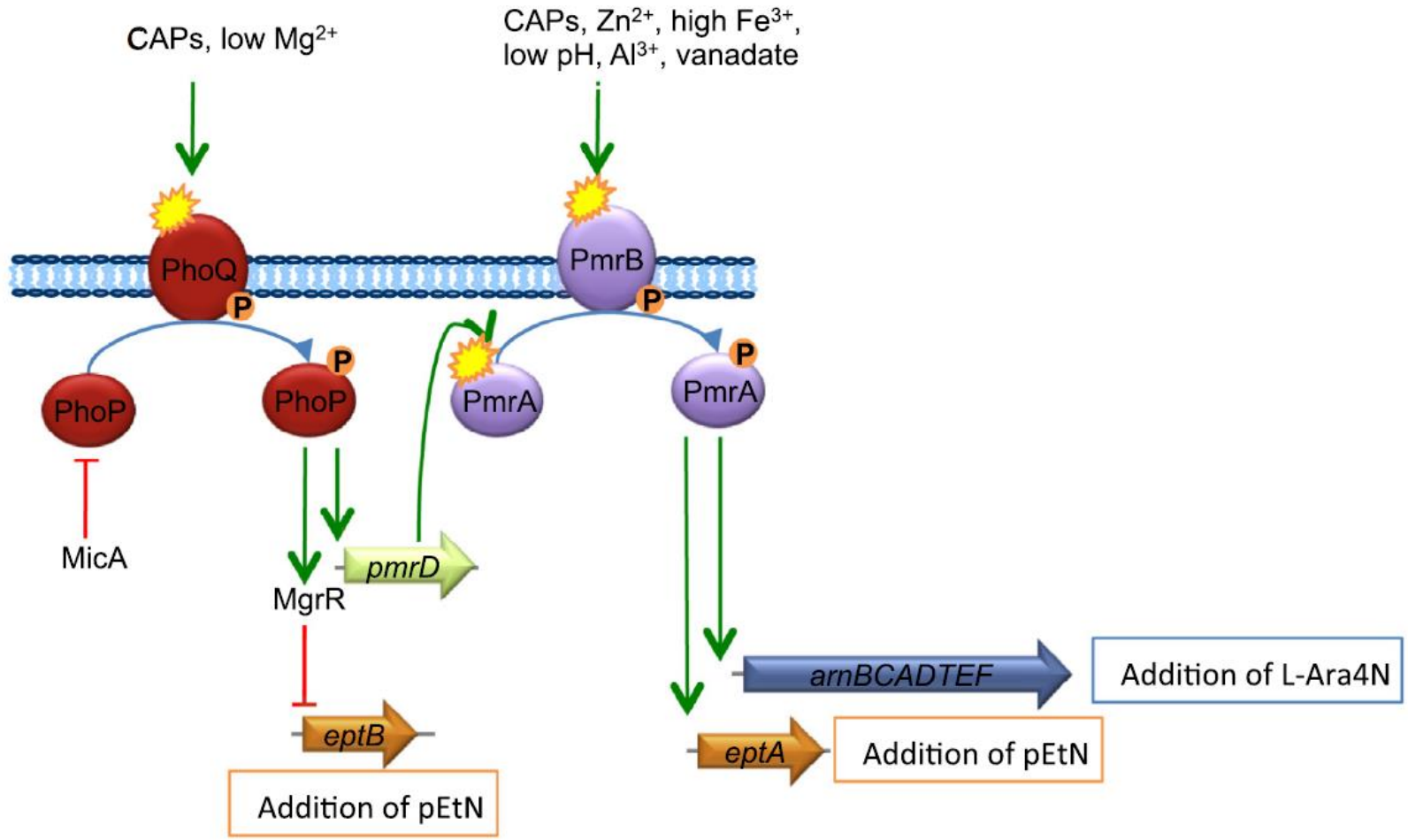
Kolistin – İntrensek Direnç

- Anaerob
- Gram-pozitif mikroorganizmalar
- *Brucella* spp.
- *Burkholderia cepacia*
- *Edwardsiella* spp.
- *Morganella morganii*
- *Proteus* spp.
- *Providencia* spp.
- *Serratia* spp.

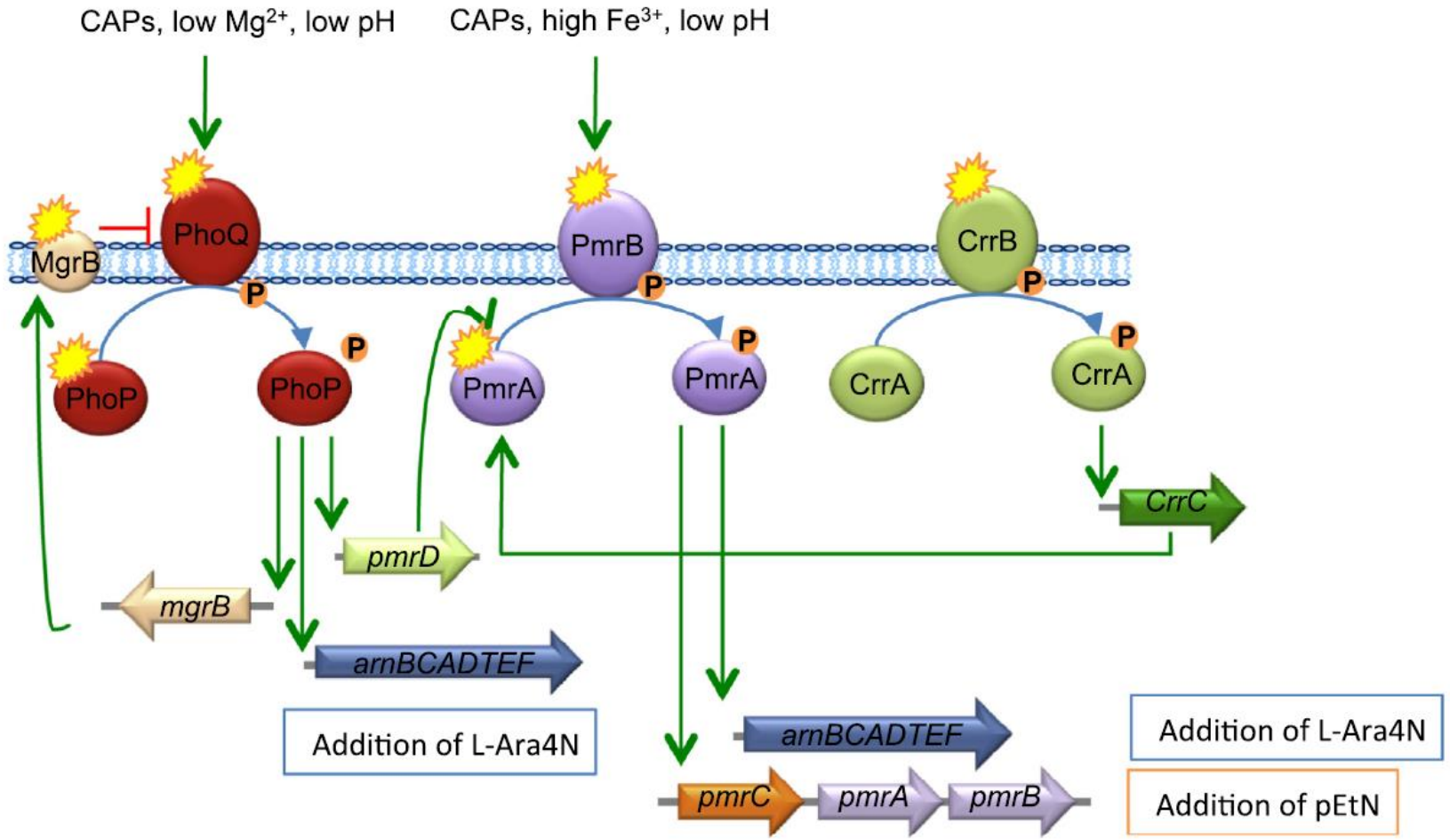
LPS yok

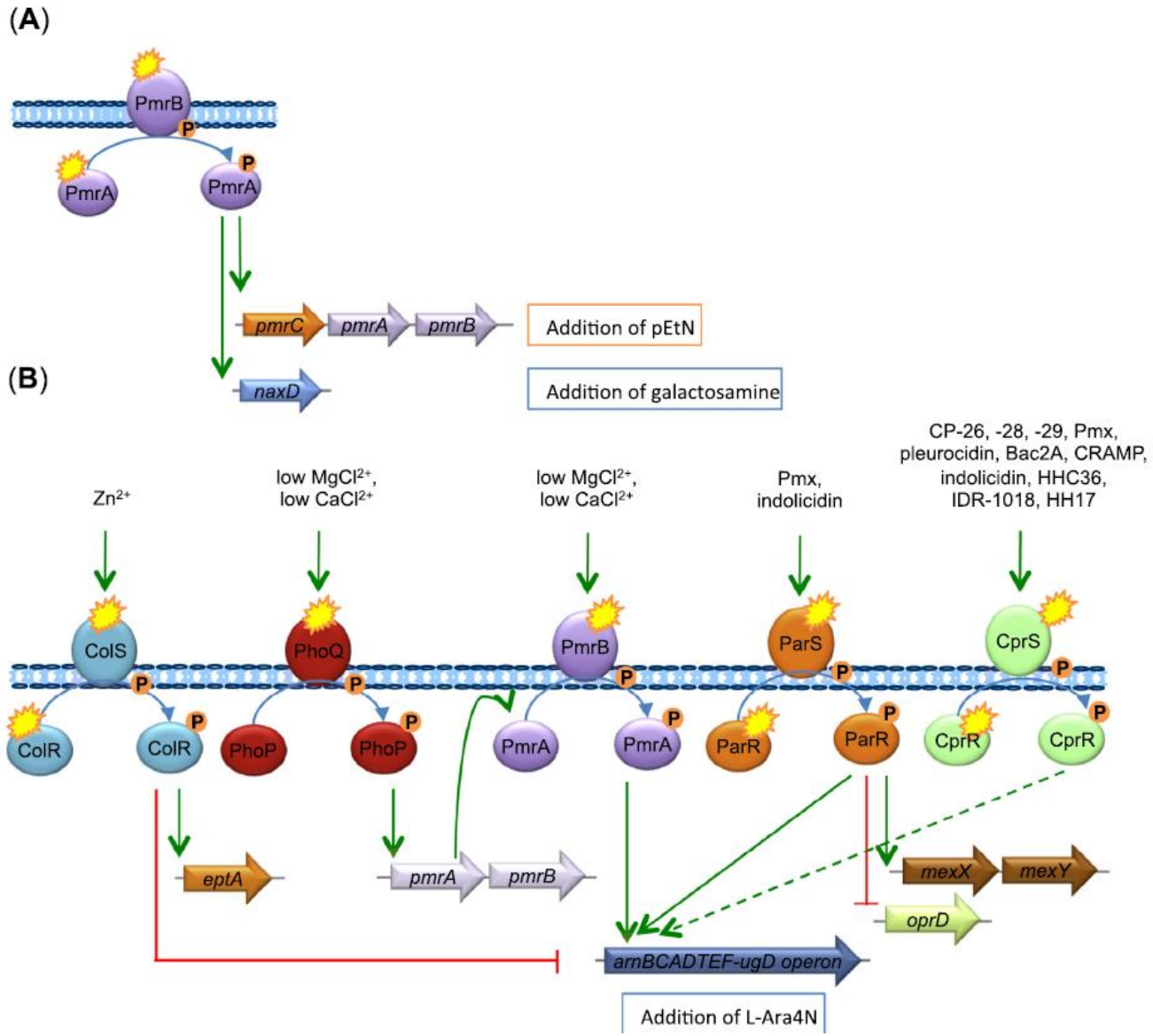
- Doğal direnç – yapısal gen ekspresyonu
  - LPS'ye katyonik moleküllerin eklenmesi
    - Kolistinin LPS'ye bağlanmasında azalma

(**A**) *E. coli*

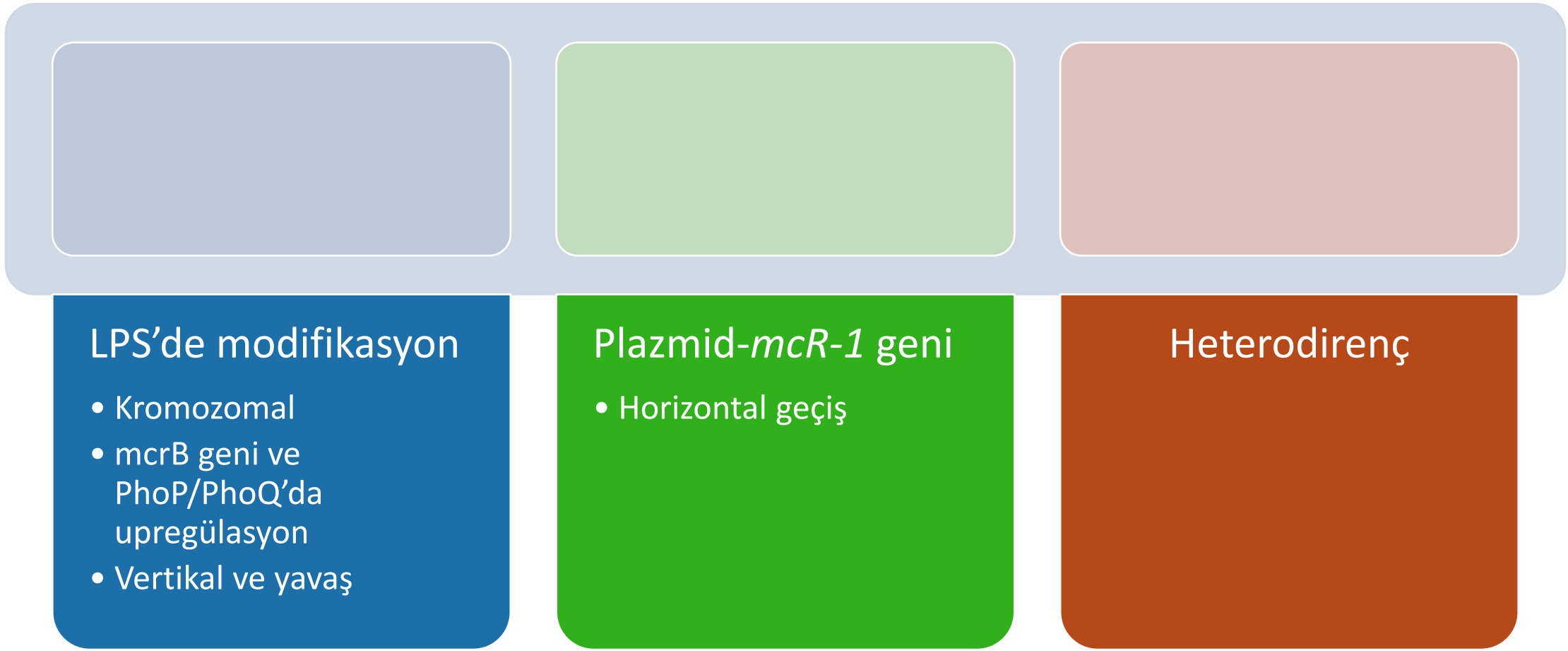

CAPs, low Mg^{2+}
CAPs, Zn^{2+}, high Fe^{3+}, low pH, Al^{3+}, vanadate
PhoQ
P
PmrB
P
PhoP
P
PhoP
P
PmrA
PmrA
P
MicA
MgrR
pmrD
eptB
Addition of pEtN
arnBCADTEF
Addition of L-Ara4N
eptA
Addition of pEtN

(**B**) *K. pneumoniae*




(A)
PmrB
P
PmrA
P
PmrA
pmrC
pmrA
pmrB
Addition of pEtN
naxD
Addition of galactosamine
(B)
Zn2+
low MgCl2+, low CaCl2+
low MgCl2+, low CaCl2+
Pmx, indolicidin
CP-26, -28, -29, Pmx, pleurocidin, Bac2A, CRAMP, indolicidin, HHC36, IDR-1018, HH17
ColS
PhoQ
PmrB
ParS
CprS
ColR
ColR
PhoP
PhoP
PmrA
PmrA
ParR
ParR
CprR
CprR
eptA
pmrA
pmrB
mexX
mexY
oprD
arnBCADTEF-ugD operon
Addition of L-Ara4N

Direnç Mekanizmaları



Current Medical Research and Opinion 2015;31:707-721
J of Global Antimicrob Resistance 2018;12:124-36

Direnç

- Dış membran porinlerinde modifikasyon ve LPS'nin negatif yükünün azalması
- Efluks pompa sistemlerinde aşırı ekspresyon
- Kapsül proteini üretimi

LPS Modifikasyonu

- Doğal dirençli gram-negatif bakterilere benzer mekanizma
- Polimiksinlere duyarlı mikroorganizmalarda mutasyon
  - LPS'de modifikasyon
- Modifikasyon
  deoxy-Dmann
  meydana gelir
  - 4-amino-4-deoxy-L-arabinose (L-Ara4N),
  - Phosphoethanolamine (PEtN)

Bakteri membranının negatif yükü azalır, sonuç olarak pozitif yüklü kolistinin bakteri membranına bağlanması azalır

Acinetobacter spp.

Lipid A’ya PEtN eklenmesi

Lipid A biyosentez genlerinin inaktivasyonu – LPS kaybı

Pseudomonas aeruginosa

Lipid A'nın negatif yüklü fosfat grubunun pozitif yüklü L-Ara4-N ve pEtN ile modifikasyonu

Multidrug efluks sistem

Klebsiella spp.

Lipid A’nın negatif yüklü fosfat grubunun pozitif yüklü L-Ara4-N ve pEtN ile modifikasyonu

Kapsüler LPS biyosentezi

Plazmid-mediated Polimiksin Direnci – mcr geni

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, BS[†], Yang Wang, PhD[†], Prof Timothy R Walsh, DSc, Ling-Xian Yi, BS, Rong Zhang, PhD, James Spencer, PhD, Yohei Doi, MD, Guobao Tian, PhD, Baolei Dong, BS, Xianhui Huang, PhD, Lin-Feng Yu, BS, Danxia Gu, PhD, Hongwei Ren,

- Çiğ et örnekleri %15
- Hayvanlar %21
- İnsanlar %1

The Lancet Infectious Diseases 2016;16:161-8

mcr geni

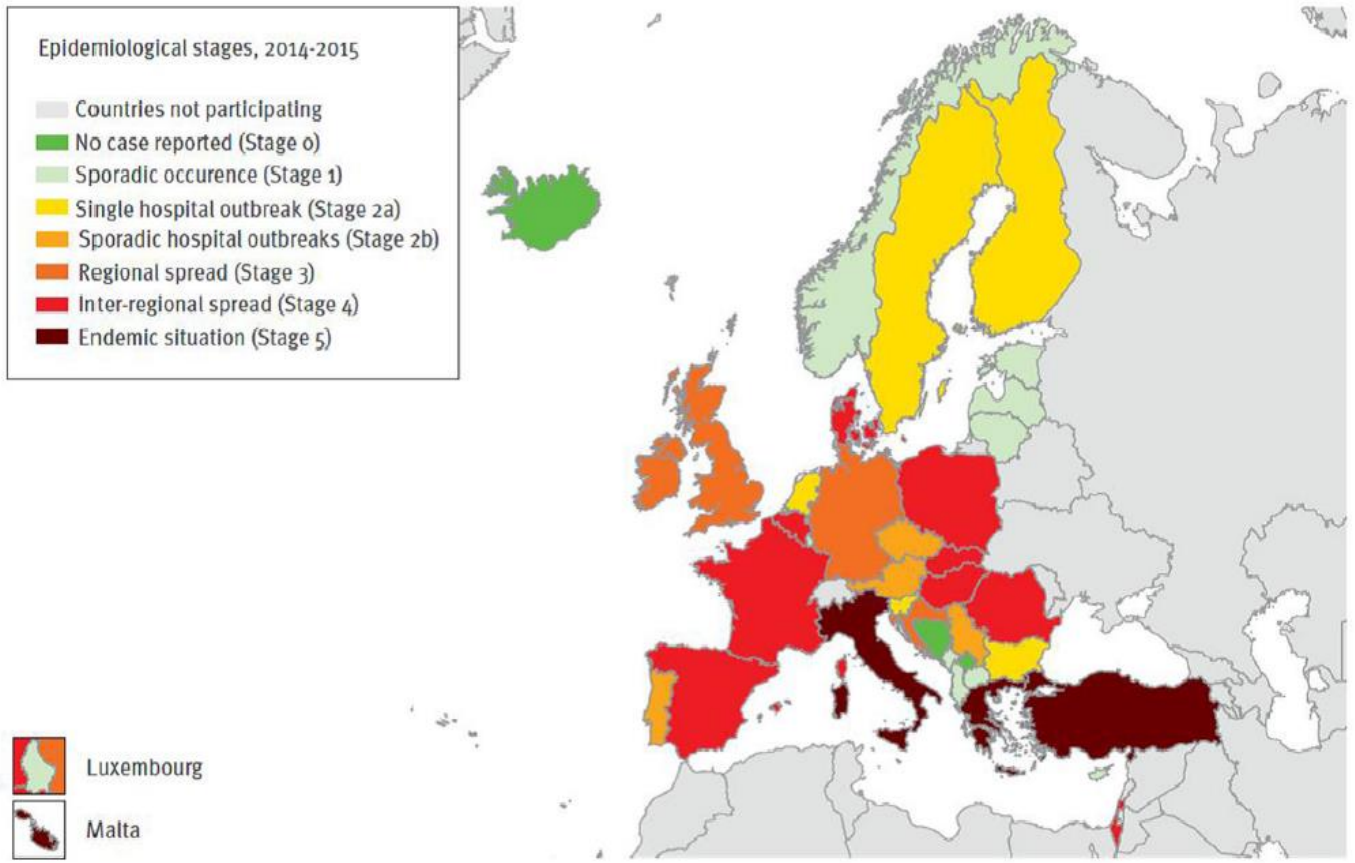
- LPS'nin Lipid A kısmına PEtN eklenmesi ile direnç
- Ocak 2016 – 19 ülkeden bildirildi
- SENTRY 2014-2015 – *E. coli* ve *K. pneumoniae* - %5
- Pandemik klonlara geçerse risk büyük
- Akılcı kullanım, seyahatte, riskli ünitelerde sürveyans

Aktarılabilir ve hızlı yayılım riski var
Türler arası transfer

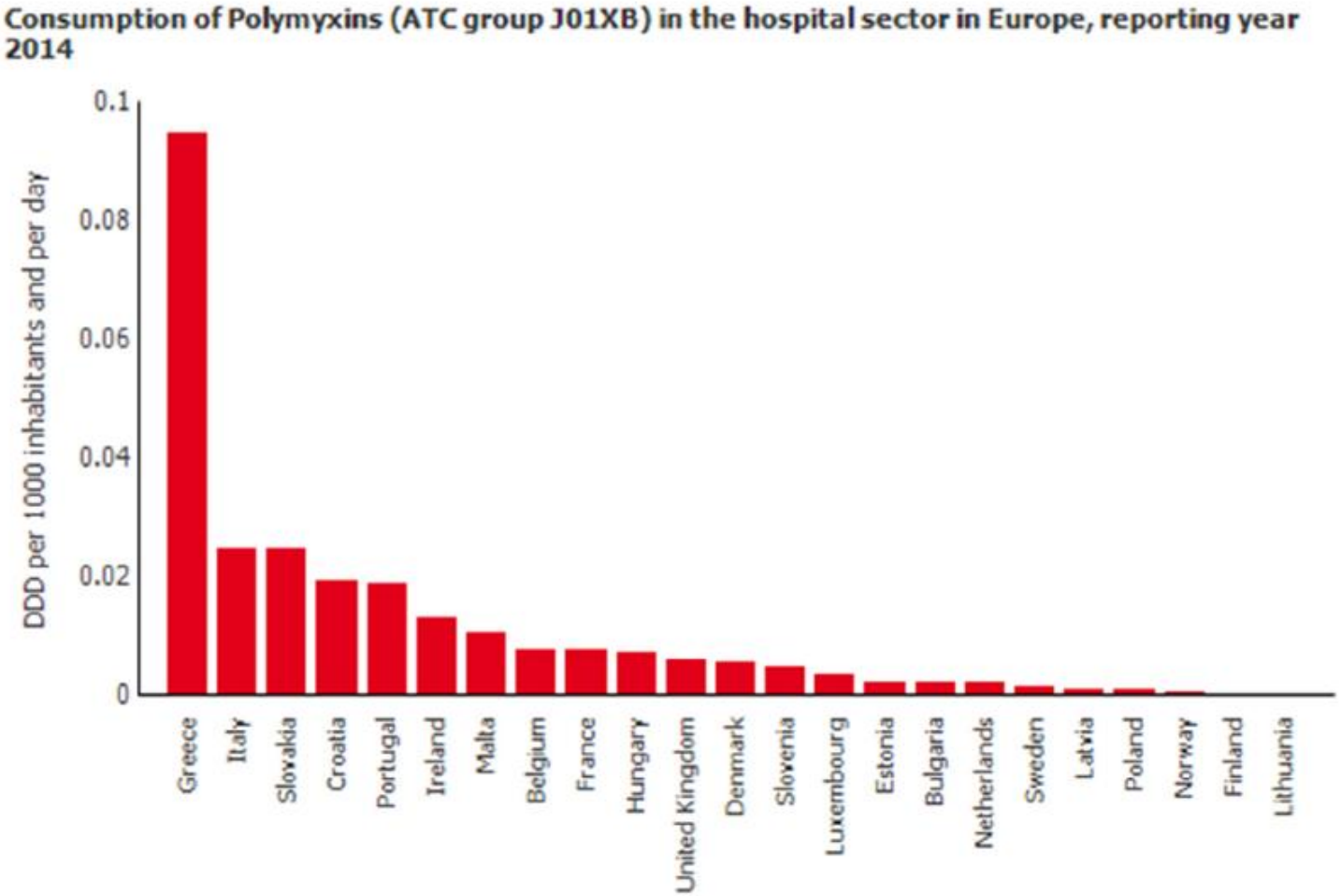
E. coli
Salmonella
Shigella
Klebsiella
Enterobacter

J of Global Antimicrob Resistance 2018;12:124-36
Lancet Infect Dis. 2016;16(3):292–3.

Karbapenemaz pozitif Enterobacteriacea ECDC – Mayıs 2015



Kolistin Kullanımı



International Journal of Antimicrobial Agents 48 (2016) 614–621

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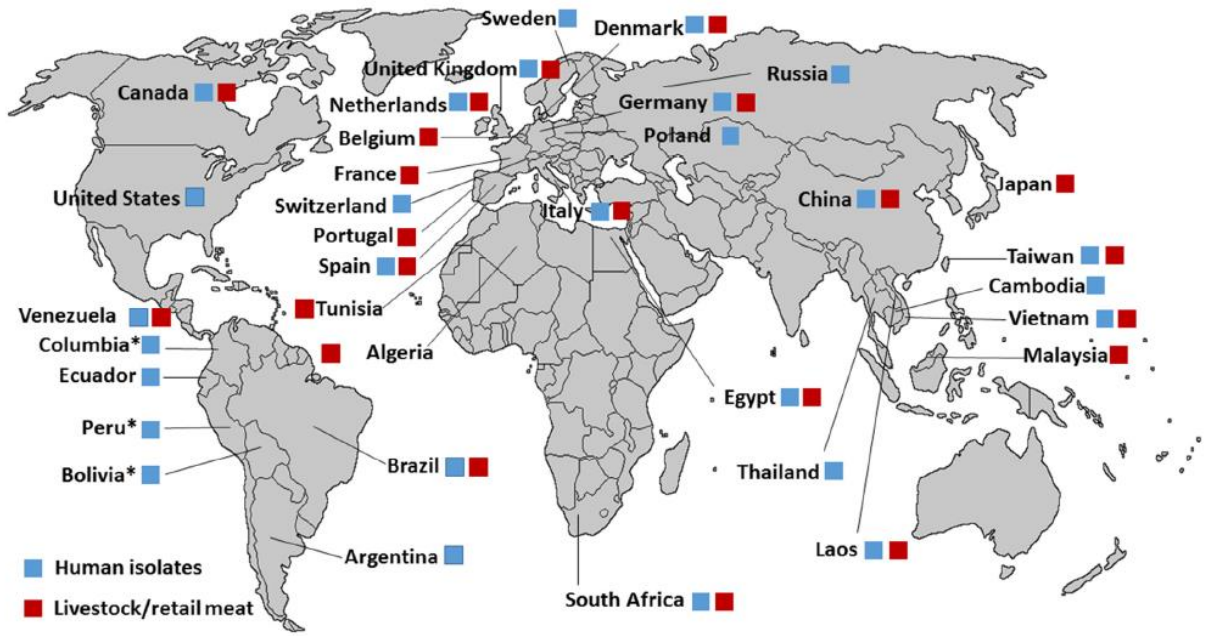
Epidemiology of infections caused by polymyxin-resistant pathogens

Helen Giamarellou [a,b,*]

[a] Internal Medicine, Athens University School of Medicine, Athens, Greece
[b] 6th Department of Internal Medicine, Hygeia General Hospital, 4 Erythrou Stavrou Str. & Kifisias Avenue, Marousi, Athens 15123, Greece



*Visited by Dutch travellers with fecal colonisation of mcr-1 gene and discovered one to two weeks after their return to the Netherlands

Mikrobiyol Bul. 2017 Jul;51(3):299-303. doi: 10.5578/mb.57515.

[Results of a multicenter study investigating plasmid mediated colistin resistance genes (mcr-1 and mcr-2) in clinical Enterobacteriaceae ısolates from Turkey].

[Article in Turkish]

Sarı AN[1], Süzük S, Karatuna O, Öğünç D, Karakoç AE, Çizmeci Z, Alışkan HE, Cömert F, Bakıcı MZ, Akpolat N, Çilli FF, Zer Y, Karataş A, Akgün Karapınar B, Bayramoğlu G, Özdamar M, Kalem F, Delialioğlu N, Aktaş E, Yılmaz N, Gürcan Ş, Gülay Z.

- Enterobacteriaceae 329 klinik izolat
- mcr-1 ve mcr-2 mevcut değil

Heterodirenç

- Standart test yöntemleriyle duyarlı olduğu düşünülen bir izolat
  - Dirençli subpopulasyon varlığı
- Populasyon analiz profil yöntemi-altın standart
  - Bakteri popülasyonu farklı antibiyotik konsantrasyonlarına maruz bırakılır
  - Her bir konsantrasyondaki üreme derecelendirilir

Table 1 Prevalence of heteroresistance to colistin or polymyxin B among Gram-negative bacilli

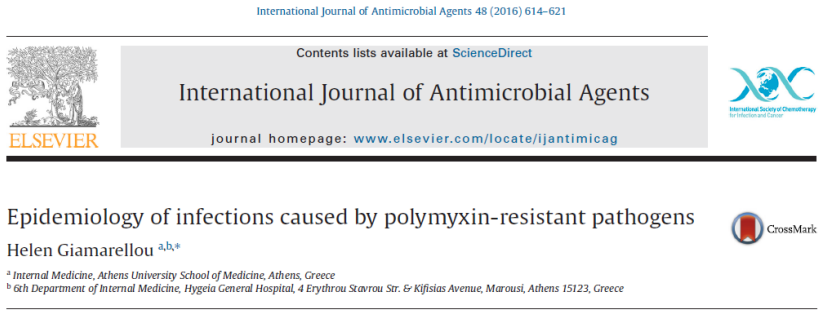
Organism	Antibiotic	Detection of heteroresistance	Year	Comments	Reference
Acinetobacter baumannii	Colistin	15/16 (93.7%)	2006	Some subpopulations were able to grow in the presence of up to 200 μg/mL of colistin	[19]
Acinetobacter baumannii--calcoaceticus complex	Colistin	19/19 (100%)	2008	Significantly higher degree of heteroresistance found among isolates from patients with previous colistin treatment. All isolates maintained colistin MICs > 16 mg/L after two passages on sheep blood plates	[20]
Acinetobacter baumannii	Colistin	13/28 (46.4%)	2009	Case report of a patient with post-neurosurgical meningitis with development of colistin resistance during intrathecal treatment	[22]
Acinetobacter baumannii *Enterobacter cloacae*	Colistin	1/7 (14%) 6/10 (60%)	2007	All isolates maintained resistance to colistin after passaging on sheep blood agar and retesting, suggesting resistance is induced upon exposure to colistin rather than via a stable mutation	[21]
Enterobacter cloacae	Polymyxin B	8/8 (100%)	2013	In several isolates, the number of heteroresistant colonies was greater at higher concentrations of polymyxin B (4–8 μg/mL) compared to lower concentrations (0.5–2 μg/mL)	[25]
Carbapenemase-producing *Klebsiella pneumoniae*	Colistin	12/16 (75%)	2011	All heteroresistant strains except one maintained colistin MICs > 8 mg/L after serial passages on colistin-free media	[26]
Pseudomonas aeruginosa	Polymyxin B	1/24 (4%)	2013	Rate of heterogeneous subpopulations with increased MICs to polymyxin B but still < 2 mg/L were 37.5% (9/24)	[24]
Burkholderia cenocepacia	Polymyxin B	–	2013	More resistant subpopulations of *B. cenocepacia* may communicate high level resistance to less resistant cells	[23]

Curr Infect Dis Rep 2017;19:38

Mikroorganizma	Çalışma/Bölge	Direnç (%)
A. baumannii	SENTRY 2001-2011	0.9-3.3
	US	0.1-4.8
	Avrupa	0.4-2.7
	Latin Amerika	0.9-1.1
	Asya Pasifik	0.7-1.7
	EARS-Net 2013	5.0 (%80'i Yunanistan)
P. aeruginosa	SENTRY 2009-2012	0.7
	SENTRY 2006-2009	0.1-0.6
	Kanada 2008-2015	5.1
	MDR ve XDR	7.1-11.7
Enterobacteriaceae		
Enterobacter spp.	SENTRY 2009-2012 (ABD, Avrupa)	13.6-15
Klebsiella spp.		2.7-3.6
E. coli		0.3-0.1
Klebsiella spp (ESBL +)		11.5-7.8
E. coli (ESBL +)		1.4-0.7

K. pneumoniae

- İlk kez 2004 Yunanistan'da direnç
- Karbapenemaz pozitif izolatlarda
  - İtalya
    - 2011 - %27.5
    - 2013-2014 - %43
  - Yunanistan
    - 2011 - %23
    - 2014 - %20
  - Kore
    - %6.8
  - Singapur
    - %6.3
- EARS 2013
  - Tüm izolatlarda %8.8
  - Karbapenemaz pozitif %32



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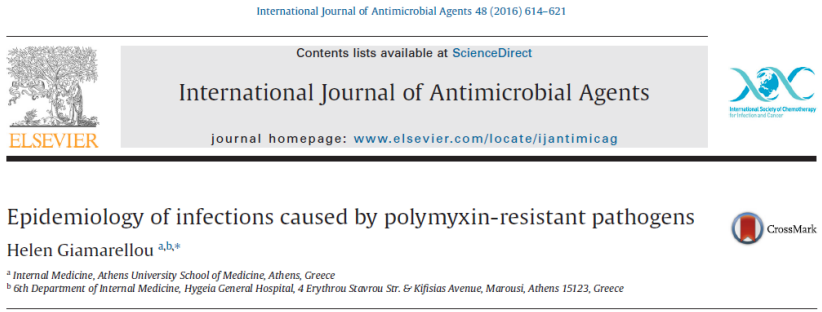
A. baumannii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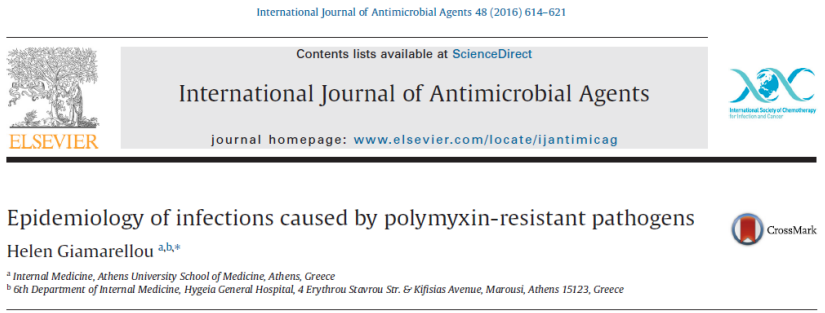
- İlk kez 1999 – Çek Cumhuriyeti
- Yunanistan 2014 - Karbapenem dirençli izolatlarda %21.1
- Bulgaristan 2005 - %16.7
- İspanya 2006 - %19.1 - %40.7
- Kore 2007 - %30.6

P. aeruginosa



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- 1998-1999 – Kistik fibrozis olgularında %50
- Kistik fibrozis dışında halen duyarlılık yüksek
  - Hindistan 2012-2013 – %2.2-3.8
  - İran 2014 - %2
  - Yunanistan 2011-2012 - %6.3
  - Avrupa 13 ülke 2011-2012 - %0.2

Journal of Hospital Infection 98 (2018) 260–263

Available online at www.sciencedirect.com

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], L. Mülazımoğlu [d], O. Ural [k], F. Can [v], H. Akalın [o], Turkish Society of Clinical Microbiology and Infectious Diseases, Healthcare-related Infections Study Group, Turkey

2014-2015
Sağlık Bakımı İlişkili Kan Dolaşımı İnfeksiyonları

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)

Journal of Global Antimicrobial Resistance 11 (2017) 10–16

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Journal of Global Antimicrobial Resistance

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

Molecular epidemiology of carbapenem-resistant *Klebsiella pneumoniae* at a Turkish centre: Is the increase of resistance a threat for Europe?

Aslıhan Candevir Ulu*, Tülin Güven Gökmen, Filiz Kibar, Behice Kurtaran, Cansu Önlen, Ferit Kuşçu, Ayşe Seza Inal, Süheyla Kömür, Akgün Yaman, Hasan Salih Zeki Aksu, Yeşim Taşova

Çukurova University Medical School, Adana, Turkey

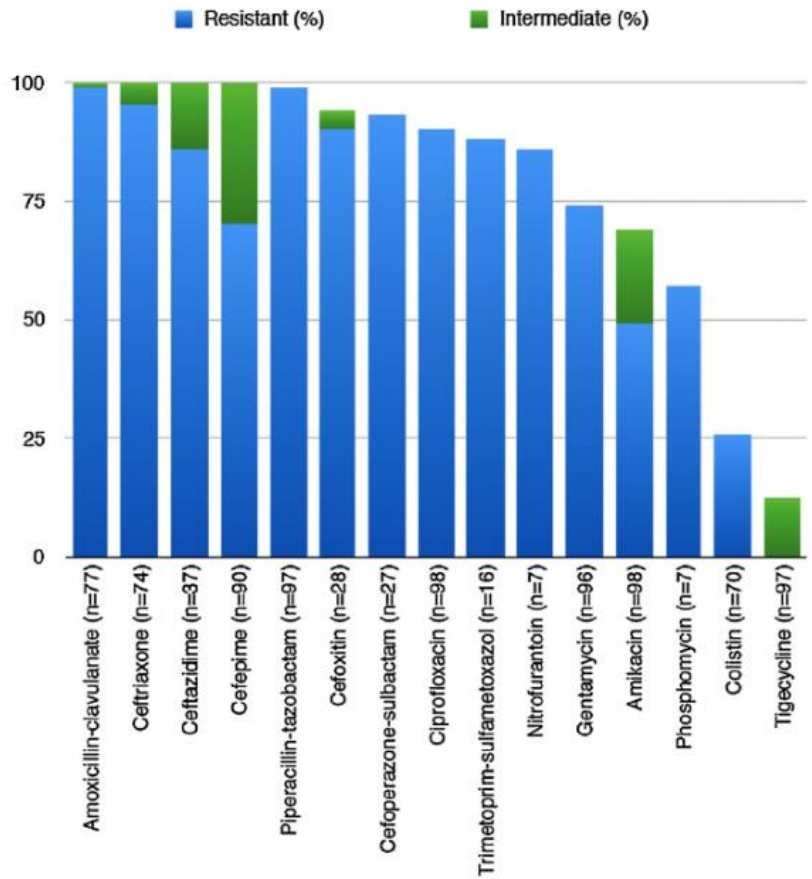

Fig. 1. Resistance and intermediate susceptibility rates of carbapenem-resistant *Klebsiella pneumoniae* isolates to various antimicrobial agents.

SDÜ Tıp Fakültesi
Araştırma ve Uygulama Hastanesi

Mikroorganizma	Karbapenem Direnci				Koistin Direnci			
	2014	2015	2016	2017	2014	2015	2016	2017
A. baumannii	97.9	100.0	97.5	96.5	1.4	1.7	3.9	1.7
K. pneumoniae	73.0	51.9	53.3	56.6	NA	0.0	30.0	29.6

Risk Faktörleri

Risk factors associated with the isolation of colistin-resistant Gram-negative bacteria: A matched case-control study

Dimitrios K. Matthaiou, MD; Argyris Michalopoulos, MD, FCCP; Petros I. Rafailidis, MD, MRCP; Drosos E. Karageorgopoulos, MD; Vassiliki Papaioannou, MD; Georgia Ntani, BSc; George Samonis, MD, PhD; Matthew E. Falagas, MD, MSc, DSc

risk factors associated with isolation of colistin-resistant *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas*

Name	CR n (%)	CS n (%)	*p* Value	CR Mean ± SD	CS Mean ± SD	*p* Value[a]
Demographics						
Age, years				57 ± 17	66 ± 19	.005
Sex (male)	23 (56.1)	32 (78)	.06			
Hospital stay,[b] days				37.1 ± 32.5	27.9 ± 36.2	.08
Comorbidities						
Heart disease	21 (51.2)	26 (63.4)	.36			
Malignancy	10 (24.4)	9 (22)	1			
COPD	10 (24.4)	14 (34.1)	.45			
Diabetes mellitus	14 (34.1)	12 (29.3)	.80			
Acute renal failure	4 (9.8)	5 (12.2)	1			
Chronic renal failure	1 (2.4)	6 (14.6)	.13			
Renal failure (total)	5 (12.2)	11 (26.8)	.21			
Liver disease	4 (9.8)	8 (19.5)	.39			
Hematological disorders	2 (4.9)	1 (2.4)	1			
Neurological disorders	7 (17.1)	12 (29.3)	.33			
Prior surgery	8 (19.5)	0 (0)	.008			
Prior hospitalization	28 (68.3)	22 (53.7)	0.24			
IC						.02
AP						0.76
Prior						
Co						<.001
An						0.14
2nd-generation cephalosporins						0.07
3rd-generation cephalosporins	21 (51.2)	18 (43.9)	0.66	6.6 ± 4.5	6 ± 4.5	0.35
Aminoglycosides	24 (58.5)	18 (43.9)	0.31	9.5 ± 8.2	7.1 ± 9.9	0.06
Quinolones	25 (61)	33 (80.5)	0.1	14.1 ± 13.5	14.8 ± 13.1	0.19
Metronidazole	13 (31.7)	17 (41.5)	0.52	12.5 ± 6.8	11.7 ± 11.3	0.88
Glycopeptides	28 (68.3)	36 (87.8)	0.23	17 ± 13	16.8 ± 17	0.50
Carbapenems	34 (82.9)	28 (68.3)	0.26	19.9 ± 17.1	16.9 ± 20.5	0.13
Monobactams	9 (22)	1 (2.4)	.02	5.3 ± 4.7	16	0.07
Antifungals	7 (17.1)	16 (39)	0.06	8.86 ± 7.13	19.81 ± 23.38	.049
β-lactams/β-lactamase inhibitors	10 (24.4)	5 (12.2)	0.23	6.2 ± 4.5	5.6 ± 5.1	.17
Invasive procedures and device placement/duration, days[c]						
Mechanical ventilation	34 (82.9)	36 (87.8)	0.73	14.3 ± 11	10.5 ± 10.6	.12
Central venous catheter	37 (90.2)	38 (92.7)	1	21 ± 15.5	18.7 ± 19.9	.51
Foley catheter	38 (92.7)	38 (92.7)	1	24.9 ± 16.8	18.9 ± 19.9	.1
Nasogastric tube	36 (87.8)	37 (90.2)	1	18.9 ± 13.6	17.6 ± 20.7	.58
Special therapies	32 (78)	24 (58.6)	0.06			
Other interventions	8 (19.5)	15 (36.6)	0.12			
Foreign material in the body	10 (24.4)	11 (26.8)	1			
Surgical operations after admission	26 (63.4)	27 (65.9)	1			
Tracheotomy	26 (63.4)	20 (48.8)	0.29	24.8 ± 30.5	20.2 ± 26.8	.12
Outcomes						
Patients with infection	35 (85.4)	36 (87.8)	1			
Patient outcome: mortality	15 (36.6)	18 (43.9)	0.58			
Infection outcome: attributable mortality	10 (24.4)	6 (14.6)	0.39			

Çok Değişkenli Analiz

Kolistin kullanımı p=0.02, OR: 7.78

Crit Care Med 2008 Vol. 36, No. 3

Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients

F. Kontopidou[1], D. Plachouras[1], E. Papadomichelakis[2], G. Koukos[1], I. Galani[1], G. Poulakou[1], G. Dimopoulos[2], A. Antoniadou[1], A. Armaganidis[2] and H. Giamarellou[1]*
1) *4th Department of Internal Medicine and* 2) *2nd Critical Care Department, University of Athens, Medical School, Athens, Greece*

In the last decade the increased incidence of infections by multidrug-resistant Gram-negative bacteria (MDR-GNB), especially in critically ill patients, restored colistin, a neglected antimicrobial, to clinical practice, as it is one of the very few and in some cases the only antimicrobial with activity against pathogens such as carbapenem-resistant *Acinetobacter* spp and carbapenemase producing *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* [1]. However, there is concern that selective pressure due to extensive colistin use may lead to the emergence of resistance. In addition, super-infection with pathogens intrinsically resistant to colistin

TABLE 2. Univariate and multivariate analysis of risk factors for colonization by CR *Klebsiella pneumoniae*

	Colonized by CRKP	Not colonized by CRKP	Univariate analysis	Multivariate analysis	Odds ratio
Age, median (range)	68 (22–86)	72 (14–89)	NS		
Gender (female/male)	11/19	54/66	NS		
APACHE II score, median (IQR)	19.5 (11.75)	18.0 (10)	NS		
Colistin treatment (%)	27 (90)	67 (56)	<0.001	<0.001	5.2
Carbapenem treatment (%)	23 (77)	81 (68)	NS		
Piperacillin/tazobactam treatment (%)	16 (53)	77 (64)	NS		
Median length of stay in ICU, days (IQR)	65 (61)	26 (32)	<0.001	NS	
Median duration of colistin treatment, days (IQR)	20.0 (17)	14.5 (23)	0.048		

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Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

Risk factors of multidrug-resistant, extensively drug-resistant and pandrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia in a Medical Intensive Care Unit of University Hospital in Thailand

Table 3
Risk factors for the occurrence of MDR, XDR and PDR-*A. baumannii* compared to DS-*A. baumannii* group by univariable polytomous logistic regression.

Risk factors	MDR		XDR		PDR	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Male gender	1.11 (0.48–2.54)	0.800	1.15 (0.55–2.39)	0.708	0.94 (0.25–3.53)	0.928
Age	1.02 (1.00–1.05)	0.055	1.01 (0.99–1.03)	0.383	1.00 (0.97–1.03)	0.973
Co morbidities						
SOFA	1.21 (1.01–1.488)	0.046	1.42 (1.18–1.70)	<0.001	1.34 (1.02–1.76)	0.037
Length of hospital stay before VAP onset >14 day	1.12 (0.45–2.77)	0.792	1.11 (0.50–2.50)	0.795	2.30 (0.59–8.90)	0.228
Mechanical ventilation days before VAP onset >14 day	3.60 (0.98–13.22)	0.070	3.30 (0.96–11.25)	0.065	1.93 (0.28–13.29)	0.503
Previous antibiotic use						
Penicillins and derivatives	2.00 (0.87–4.61)	0.104	1.61 (0.77–3.35)	0.205	2.4 (0.60–9.56)	0.214
Third generation Cephalosporins	0.66 (0.27–1.64)	0.374	0.58 (0.26–1.32)	0.195	0.75 (0.18–3.11)	0.692
Fluoroquinolones	3.03 (1.11–8.27)	0.030	2.94 (1.17–7.42)	0.022	6.30 (1.48–26.83)	0.013
Aminoglycosides	5.96 (1.30–27.26)	0.021	2.35 (0.53–10.36)	0.258	5.17 (0.74–35.84)	0.097
Carbapenems	6.00 (1.67–21.56)	0.006	6.92 (2.05–23.37)	0.002	30.00 (5.13–175.27)	<0.001
Vancomycin	1.40 (0.27–7.38)	0.685	4.67(1.08–20.27)	0.039	5.17 (0.74–35.84)	0.097
Colistin	0.45(0.03–7.43)	0.577	1.52 (0.20–12.30)	0.693	96.0 (8.87–1038.23)	<0.001

Table 4
Risk factors for the occurrence of MDR, XDR and PDR-*A. baumannii* compared to DS-*A. baumannii* group by multivariable polytomous logistic regression.

	MDR		XDR		PDR	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
SAPS II	1.01 (0.97–1.05)	0.485	1.01 (0.97–1.05)	0.698	1.10 (1.01–1.22)	0.046
SOFA	1.14 (0.89–1.47)	0.298	1.35 (1.07–1.71)	0.011	0.99 (0.64–1.52)	0.958
Previous antibiotic use						
Carbapenems	5.20 (1.41–19.17)	0.013	6.30 (1.80–21.97)	0.004	12.84 (1.60–103.20)	0.016
Colistin	0.46 (0.02–8.62)	0.608	1.61 (0.16–16.15)	0.687	155.95 (8.00–3041.98)	0.001

Risk factors for bloodstream infections due to colistin-resistant KPC-producing *Klebsiella pneumoniae*: results from a multicenter case–control–control study

D. R. Giacobbe[1], V. Del Bono[1], E. M. Trecarichi[2], F. G. De Rosa[3], M. Giannella[4], M. Bassetti[5], A. Bartoloni[6], A. R. Losito[2], S. Corcione[3], M. Bartoletti[4], E. Mantengoli[6], C. Saffioti[1], N. Pagani[3], S. Tedeschi[4], T. Spanu[7], G. M. Rossolini[8,9,10], A. Marchese[11], S. Ambretti[12], R. Cauda[2], P. Viale[4], C. Viscoli[1] and M. Tumbarello[2], for ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

1) *Infectious Diseases Division, University of Genoa (DISSAL) and IRCCS San Martino-IST, Genoa,* 2) *Institute of Infectious Diseases, Catholic University of the Sacred Heart, A. Gemelli Hospital, Rome,* 3) *Department of Infectious Diseases, Amedeo di Savoia Hospital, U*
Diseases, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, 5) *Infectious Disease Division, Santa Ma*

TABLE 1. Univariate analysis of risk factors for BSI caused by colistin-resistant KPC-Kp (case group) compared to control patients without infections caused by KPC-Kp (control group A) and control patients with BSI caused by colistin-susceptible KPC-Kp (control group B)

Variable	Case group (n = 142)	Control group A (n = 284)	Case group vs. control group A		Control group B (n = 284)	Case group vs. control group B	
			OR (95% CI)	p		OR (95% CI)	p
Age (years), median (IQR)	66 (54–74)	70 (54–78)	—	0.06	67 (55–77)	—	0.23
Male sex	89 (62.7)	164 (57.7)	1.23 (0.80–1.90)	0.33	180 (63.4)	0.97 (0.63–1.51)	0.89
Comorbidities							
COPD	14 (9.9)	46 (16.2)	0.56 (0.28–1.10)	0.08	41 (14.4)	0.65 (0.31–1.27)	0.18
Biliary devices	1 (0.7)	5 (1.8)	0.39 (0.01–3.59)	0.38	7 (2.5)	0.28 (0.01–2.22)	0.21
Cardiovascular diseases	53 (37.3)	130 (45.8)	0.70 (0.46–1.09)	0.10	120 (42.2)	0.81 (0.52–1.25)	0.33
Cerebrovascular diseases and dementia	15 (10.6)	43 (15.1)	0.66 (0.33–1.27)	0.19	35 (12.3)	0.84 (0.41–1.65)	0.59
				0.28	50 (17.6)	1.05 (0.59–1.82)	0.86
				0.004	43 (15.1)	1.26 (0.70–2.21)	0.40
				0.60	71 (25.0)	0.80 (0.48–1.33)	0.37
				0.75	4 (1.4)	1 (0.09–7.07)	1.00
				0.27	54 (19.0)	0.82 (0.46–1.44)	0.48
				0.09	27 (9.5)	0.96 (0.44–2.00)	0.91
				0.38	13 (4.6)	0.45 (0.08–1.68)	0.21
				<0.001	21 (7.4)	1.26 (0.56–2.74)	0.53
				<0.001	39 (13.7)	2.25 (1.50–4.31)	<0.001
				<0.001	.	1.24 (0.80–1.93)	0.32
				<0.001	121 (42.6)	1.69 (1.10–2.59)	0.01
				<0.001	60 (21.1)	1.91 (1.18–3.06)	0.005
				<0.001	36 (12.7)	1.84 (1.04–3.25)	0.02
				0.006	26 (9.1)	1.17 (0.56–2.39)	0.64
				0.03	19 (6.7)	1.29 (0.55–2.89)	0.51
				0.63	49 (17.2)	1.39 (0.81–2.36)	0.19
				0.59	19 (6.7)	0.30 (0.06–1.05)	0.04
				<0.001	54 (19.0)	1.56 (0.94–2.57)	0.07
				0.48	2 (0.7)	2.01 (0.14–28.00)	0.48
				0.03	42 (14.8)	0.89 (0.47–1.64)	0.69
				<0.001	93 (32.7)	1.83 (1.19–2.83)	0.004
				0.26	13 (4.6)	0.76 (0.21–2.33)	0.61
				<0.001	20 (7.0)	1.22 (0.52–2.71)	0.60
				1.00	3 (1.1)	0.66 (0.01–8.36)	0.72
				<0.001	49 (17.2)	2.69 (1.64–4.37)	<0.001
				0.006	37 (13.0)	0.85 (0.42–1.63)	0.60
				<0.001	175 (61.6)	1.34 (0.86–2.11)	0.17
				<0.001	61 (21.5)	1.53 (0.94–2.48)	0.06
				0.13	51 (18.0)	0.79 (0.43–1.41)	0.41
				0.002	159 (56.0)	1.17 (0.76–1.80)	0.45
				0.22	30 (10.6)	0.93 (0.44–1.88)	0.82
				0.72	98 (34.5)	0.97 (0.62–1.51)	0.88
				<0.001	41 (14.4)	1.03 (0.55–1.87)	0.92
				0.05	83 (29.2)	0.68 (0.41–1.11)	0.10
Immunosuppressive therapy	18 (12.7)	12 (4.2)	3.29 (1.44–7.71)	0.001	25 (8.8)	1.50 (0.74–2.99)	0.21
Corticosteroid therapy	22 (15.5)	42 (14.8)	1.06 (0.57–1.91)	0.85	46 (16.2)	0.95 (0.52–1.70)	0.85
Chemotherapy/radiotherapy	18 (12.7)	69 (24.3)	0.45 (0.24–0.81)	0.005	39 (13.7)	0.91 (0.47–1.71)	0.76
PEG	4 (2.8)	5 (1.8)	1.62 (0.31–7.63)	0.47	8 (2.8)	1.00 (0.22–3.81)	1.00
Bedridden	30 (21.1)	64 (22.5)	0.92 (0.54–1.54)	0.74	51 (18.0)	1.22 (0.71–2.08)	0.43
Previous surgery	63 (44.4)	72 (25.3)	2.35 (1.50–3.67)	<0.001	120 (42.2)	1.09 (0.71–1.67)	0.68
Recent antibiotic therapy							
In general	119 (83.8)	210 (73.9)	1.82 (1.06–3.21)	0.02	240 (84.5)	0.95 (0.53–1.73)	0.85
By classes							
Aminoglycosides	15 (10.6)	13 (4.6)	2.46 (1.05–5.79)	0.02	30 (10.6)	1.00 (0.48–2.00)	1.00
β-Lactam-β-lactamase inhibitor	53 (37.3)	109 (38.4)	0.96 (0.62–1.48)	0.83	150 (52.8)	0.53 (0.34–0.82)	0.002
Fluoroquinolones	47 (33.1)	87 (30.6)	1.12 (0.71–1.76)	0.60	95 (33.4)	0.98 (0.62–1.54)	0.94
Oxyiminocephalosporins	19 (13.4)	70 (24.6)	0.47 (0.26–0.84)	0.007	38 (13.4)	1.00 (0.52–1.87)	1.00
Carbapenems	45 (31.7)	33 (11.6)	3.53 (2.06–6.05)	<0.001	92 (32.4)	0.97 (0.61–1.52)	0.88
Glycopeptides	39 (27.5)	37 (13.0)	2.53 (1.47–4.32)	<0.001	62 (21.8)	1.35 (0.83–2.21)	0.20
Colistin	40 (28.2)	6 (2.1)	18.17 (7.31–53.62)	<0.001	15 (5.3)	7.03 (3.60–14.25)	<0.001
Other	49 (34.5)	61 (21.5)	1.93 (1.20–3.08)	0.004	80 (28.2)	1.34 (0.85–2.11)	0.18

TABLE 2. Multivariate analysis of risk factors for BSI caused by colistin-resistant KPC-Kp[a]

Control group and risk factors	OR (95% CI)	p
Control group A (patients without KPC-Kp infection)[b]		
Previous colistin administration	24.51 (8.75–68.67)	<0.001
Previous colonization with KPC-Kp	18.71 (8.05–43.51)	<0.001
Previous ≥3 hospitalization	5.32 (2.48–11.38)	<0.001
Charlson score ≥3	2.84 (1.52–5.29)	0.001
Neutropenia	2.72 (1.02–7.23)	0.04
Control group B (patients with BSI due to colistin-susceptible KPC-Kp)[c]		
Previous colistin administration	6.88 (3.55–13.34)	<0.001
Previous colonization with KPC-Kp	2.40 (1.46–3.97)	0.001
Charlson score ≥3	2.97 (1.74–5.06)	<0.001

original article

Risk factors for infection with colistin-resistant gram-negative microorganisms: a multicenter study

Gul R. Yilmaz,[a] Murat Dizbay,[b] Tumer Guven,[c] Husnu Pullukcu,[d] Meltem Tasbakan,[d] Ozlem Tunccan Guzel,[b] Yasemin T. Tekce,[e] Mehmet Ozden,[f] Ozge Turhan,[g] Rahmet Guner,[c] Yasemin Cag,[h] Fatma Bozkurt,[i] Fatma Yilmaz Karadag,[j] Elif Doyuk Kartal,[k] Gokhan Gozel,[l] Cemal Bulut,[m] Sebnem Erdinc,[m] Siran Keske,[n] Ziya Cibali Acikgoz,[o] Mehmet A. Tasyaran[c]

Son 3 ayda kinolon kullanımı 3.2 kat (P=.003, 95% CI:1.50-6.74)
Son 3 ayda kolistin kullanımı 3.6 kat (P<0.01, 95%CI:1.63-7.99)

Ann Saudi Med 2016; 36(3): 216-222

Table 2. Univariate analysis of risk factors as invasive devices and antibiotic usage associated with infection of colistin-resistant gram-negative microorganisms and prognosis.

Invasive devices and treatment	Colistin S n=109 (%)	Colistin R n=56 (%)	P
Mechanical ventilation	71 (65.1)	39 (69.6)	.56
Central venous catheter	79 (72.5)	40 (71.4)	.89
Urinary catheter	91 (83.5)	45 (80.4)	.38
Steroid use	18 (16.5)	14 (25.0)	.21
Hemodialysis	13 (12.0)	12 (21.4)	.09
H2 receptor blocker or proton pump inhibitor use	89 (81.7)	48 (85.7)	.33
Total parenteral nutrition	55 (50.5)	30 (53.6)	.70
Nasogastric entubation	67 (61.5)	36 (64.3)	.43
Previous antibiotic use (last 3 months)	73 (67.0)	49 (87.5)	.003
Colistin	16(14.7)	17 (30.4)	.016
Carbapenem	38 (34.9)	29 (51.8)	.027
Glycopeptide	25 (22.9)	11 (19.6)	.39
Cephalosporin	39 (35.8)	25 (44.6)	.17
Aminoglycoside	7 (6.4)	4 (7.1)	1.00
Quinolone	19 (17.4)	24 (42.9)	.001
Sulbactam	24 (22.0)	17 (30.4)	.16
Tigecycline	10 (9.2)	13 (23.2)	.15
Piperacillin-tazobactam	32 (29.4)	22 (39.3)	.13
Metronidazole	18 (16.5)	8 (14.3)	.45
Linezolide/daptomycine	21 (19.3)	18 (32.1)	.051
Anti-fungal agent	19 (17.4)	12 (21.4)	.33
Clinical cure	63(57.8)	27 (48.2)	.24
Microbiological cure	61 (65.6)	29 (51.8)	.07
Length of hospital stay before MDR infection (median, minimum-maximum)	14 (3-148)	21 (3-118)	.04

Tedavi??? Ne Kullanalım??!

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Published online 2018 January 28. Research Article

Colistin-Resistant *Klebsiella pneumoniae*: Prevalence of Integrons and Synergistic Out Turn for Colistin-Meropenem

Prasanth Manohar,[1] Thamaraiselvan Shanthini,[1] Pandey Ekta,[1] Mahesan J B,[1] Kodiveri Muthukaliannan Gothandam,[1] Bulent Bozdogan,[2] and Nachimuthu Ramesh[1,*]

- 24 *K. pneumoniae* (kolistin R)
- Kolistin ve meropenem sinerjik etki?
- Sonuçlar
  - Checkerboard %86
  - Time-kill %76
  - Modifiye time-kill %94
- Yorum
  - Kolistin + meropenem: Bakterisidal etkili

ARTICLE IN PRESS

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International Journal of Antimicrobial Agents

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

New therapy from old drugs: synergistic bactericidal activity of sulfadiazine with colistin against colistin-resistant bacteria, including plasmid-mediated colistin-resistant mcr-1 isolates

Liliane Okdah [1], Stéphanie Le Page [1], Abiola Olumuyiwa Olaitan, Grégory Dubourg, Linda Hadjadj, Jean-Marc Rolain *

Aix-Marseille Université, IRD, APHM, MEPHI, IHU Méditerranée Infection, Marseille, France

- 53 kolistin R klinik izolat
  - *Klebsiella pneumoniae* (n = 27)
  - *Serratia marcescens* (n = 1)
  - *Proteus vulgaris* (n = 1)
  - *Escherichia coli* (n = 24)
- E test ve «checkerboard»la sinerji
  - Kolistin + sülfadiazin %92.7
  - Kolistin + SMX %33.3
  - Kolistin + TMP %47.3
  - Kolistin + SXT %31.5

29 *mcr*-1 geni pozitif

AAC
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In Vitro Synergy of Colistin Combinations against Colistin-Resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* Isolates

Céline Vidaillac,[a,b]* Lothaire Benichou,[a] and Raphaël E. Duval[a,b]
SRSMC, UMR CNRS 7565[a] and ABC Platform,[b] Université de Lorraine, Nancy, France

- *A. baumannii* (12)
- *P. aeruginosa* (4)
- *K. pneumoniae* (4)
- Kolistin + TMP veya TMP/SMX veya vankomisin
- Tüm kombinasyonlar sinerjik ve/veya bakterisidal

Antimicrobial Agents and Chemotherapy 2012;9:4856-4861

Infection and Drug Resistance

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ORIGINAL RESEARCH

In vitro activity of colistin mono- and combination therapy against colistin-resistant *Acinetobacter baumannii*, mechanism of resistance, and clinical outcomes of patients infected with colistin-resistant *A. baumannii* at a Thai university hospital

- 2011- 2015 arası 17 kolistin-R klinik izolat
- %35.3 olgu – pnömoni
- 30 gün mortalitesi %70.6
- Tüm izolatlar tigesikline duyarlı
- Sinerji
  - Kolistin + imipenem/meropenem %16.7
  - Sulbaktam %66.7
  - Tigesiklin %66.7

Infection and Drug Resistance 2017:10

Table 3 Characteristics and outcomes of patients infected with colistin-resistant *Acinetobacter baumannii*

Patient number	Age (years)	Sex	Comorbidity	Diagnosis	ICU	Septic shock	Prior colistin use	Regimen	Treatment duration (days)	Clinical outcome
1	58	M	DM	VAP	Yes	Yes	No	COL IMP	14	Improvement
2	81	M	DM, ESRD with HD	VAP	Yes	Yes	Yes	SUL LVX	5	Death
3	67	M	SCLC, RF	VAP	Yes	Yes	Yes	COL FOS	14	Death
4	91	F	PAD, HT, DLP, RF	Septicemia	Yes	Yes	No	COL SUL	11	Death
5	61	M	BPH, HT, RF	UTI	No	No	No	COL SUL	10	Improvement
6	90	F	HT, RF	Bacterial peritonitis	Yes	Yes	Yes	COL IMP	3	Death
7	77	M	DM, CA	Cholangitis	No	Yes	No	COL IMP	14	Death
8	81	M	HT, COPD	HAP	No	Yes	No	COL IMP	17	Improvement
9	63	F	DM, HD	Cellulitis	Yes	Yes	Yes	COL IMP	13	Death
10	82	M	HT, RF	VAP	Yes	Yes	Yes	COL MEP	12	Death
11	21	M	AKI with CVVHDF	Septicemia	Yes	Yes	No	COL MEP	4	Death
12	55	M	ALL, AKI	Septicemia	Yes	Yes	No	COL IMP	11	Death
13	80	F	HT, DM	Septicemia	No	Yes	No	COL IMP	21	Cure
14	83	M	HT, DM	Cholangitis, septicemia	No	Yes	No	COL IMP	18	Cure
15	63	F	DM	Cholangitis, septicemia	No	Yes	No	COL FOS	10	Death
16	76	M	HT, ESRD with HD	Septicemia	Yes	Yes	No	COL IMP	11	Death
17	85	F	AKI with HD	VAP with pleural effusion	Yes	Yes	No	TIG SUL	25	Death

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

In vitro antimicrobial synergy of colistin with rifampicin and carbapenems against colistin-resistant *Acinetobacter baumannii* clinical isolates

Duck Jin Hong [a,b], Jung Ok Kim [b], Hyukmin Lee [b], Eun-Jeong Yoon [b], Seok Hoon Jeong [b,*], Dongeun Yong [b], Kyungwon Lee [b]

[a] Department of Laboratory Medicine, Eone Reference Laboratory, Incheon, Seoul, Republic of Korea
[b] Department of Laboratory Medicine and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, Republic of Korea

- 2012-2014 arasında 41 kol R, 41 kol S klinik izolat
- E test MIC/MIC oranı metodu
- Sinerjistik aktivite
  - Kolistin+ rifampisin
    - %80.5 vs. %14.6, P< 0.0001
  - Kolistin + meropenem
    - %85.4 vs. %4.9, P< 0.0001
  - Kolistin-imipenem
    - %46.3 vs. %2.4, P< 0.0001

International Journal of Antimicrobial Agents 49 (2017) 321–326

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International Journal of Antimicrobial Agents

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Synergy against extensively drug-resistant *Acinetobacter baumannii* in vitro by two old antibiotics: colistin and chloramphenicol

Wen-juan Wei [a], Hai-fei Yang [b,c,*,1]

[a] Department of Microbiology and Immunology, Southeast University School of Medicine, Nanjing, China
[b] Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China
[c] Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China

- Kolistin R 2 suşta bakterisid ve sinerjik

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Indian J Crit Care Med. 2017 May; 21(5): 317–321.
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A Study of 24 Patients with Colistin-Resistant Gram-negative Isolates in a Tertiary Care Hospital in South India

Rajalakshmi Arjun, Ram Gopalakrishnan, P. Senthur Nambi, D. Suresh Kumar, R. Madhumitha, and V. Ramasubramanian

Department of Infectious Diseases, Apollo Hospitals, Chennai, Tamil Nadu, India
Address for correspondence: Dr. Rajalakshmi Arjun, #6, Padma Nagar, Fort, Trivandrum - 695 023, Kerala, India. E-mail: dr.a.rajalakshmi@gmail.com

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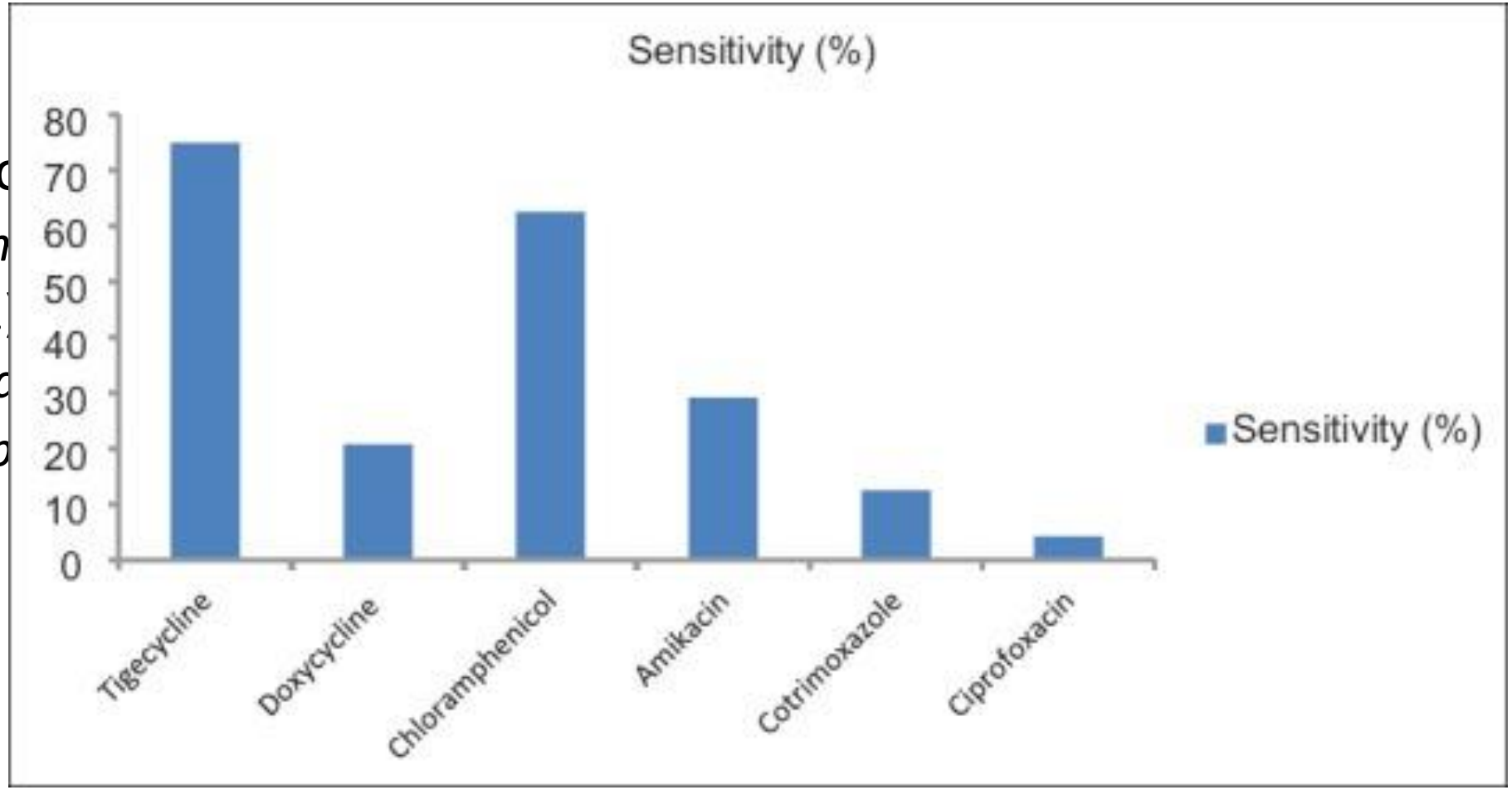

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Address for correspondence: Dr. Rajalakshmi Arjun, #6, Padma Nagar, Fort, Trivandrum - 695 023, Kerala, India. E-mail: dr.a.rajalakshmi@gmail.com

Table 1

Patient profile, antibiotic combination used, and outcome

Serial number	APACHE score	Charlson index	Sample	Antibiotics used for treatment	Clearance on surveillance cultures	Outcome
1	22	6	Blood	Tigecycline + co-trimoxazole	Not checked	Expired
2	24	9	Blood	Tigecycline + ciprofloxacin	Not checked	Discharged
3	12	5	Blood	Chloramphenicol + fosfomycin + doripenem	Not checked	Expired
4	25	7	Blood	Tigecycline + chloramphenicol	Not checked	Expired
5	12	5	Blood	Tigecycline + ciprofloxacin	Cleared	Expired
6	16	3	Blood	Chloramphenicol + fosfomycin	Not checked	Expired
7	10	8	Urine	Chloramphenicol + fosfomycin	Cleared	Expired
8	25	1	Urine	Chloramphenicol + fosfomycin+ imipenem	Not checked	Discharged
9	4	7	Urine	Tigecycline + chloramphenicol + colistin	Not checked	Expired
10	15	1	Respiratory	Tigecycline + colistin	Not checked	Lost to follow-up
11	18	4	Respiratory	Tigecycline + colistin	Not checked	Lost to follow-up
12	25	7	Respiratory	Tigecycline + colistin	Not checked	Expired
13	12	7	Pus	Tigecycline	Not checked	Discharged
14	2	5	Pus	Tigecycline + co-trimoxazole	Not checked	Lost to follow-up
15	12	3	Pus	Tigecycline + amikacin + colistin	Not checked	Expired
16	9	7	CSF	Tigecycline + chloramphenicol + sulbactum	Not checked	Expired

CSF: Cerebrospinal fluid; APACHE: Acute Physiology and Chronic Health Evaluation

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ORIGINAL ARTICLE BACTERIOLOGY

Bactericidal and synergistic activity of double-carbapenem regimen for infections caused by carbapenemase-producing *Klebsiella pneumoniae*

A. Oliva, F. Gizzi, M. T. Mascellino, A. Cipolla, A. D'Abramo, C. D'Agostino, V. Trinchieri, G. Russo, F. Tierno, M. Iannetta, C. M. Mastroianni and V. Vullo

Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

- 15 sepsis, ciddi sepsis, septik şok
- Yüksek doz meropenem + ertapenem
- Klinik/mikrobiyolojik yanıt %80
- Sinerji %78.6

Clin Microbiol Infect 2016; 22: 147–153

Bactericidal and synergistic activity of double-carbapenem regimen for infections caused by carbapenemase-producing *Klebsiella pneumoniae*

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TABLE 2. ***In vitro*** **susceptibility of carbapenem-resistant** ***Klebsiella pneumoniae*** **throughout the VITEK-2 system**

Strains (n = 15)	MEM VITEK-2 mg/L	MEM BMD mg/L	ERT VITEK-2 mg/L	ERT BMD mg/L	FQ VITEK-2 mg/L	Gentamicin VITEK-2 mg/L	COL VITEK-2 mg/L	TIG VITEK-2 mg/L
1	>16	256	>8	256	>4	8	>16	4
2	>16	512	>8	128	>4	<1	<0.5	4
3	>16	512	>8	256	>4	4	>16	2
4	>16	512	>8	256	>4	<1	<0.5	2
5	>16	128	>8	256	>4	4	>16	1
6	>16	128	>8	256	>4	2	>16	1.5
7	>16	128	>8	256	>4	4	>16	4
8	>16	256	>8	256	>4	8	<2	<1
9	>16	32	>8	64	>4	4	>16	2
10	>16	128	>8	128	>4	4	<0.5	4
11	>16	ND	>8	ND	>4	<1	<0.5	4
12	>16	256	>8	128	>4	4	>16	4
13	>16	256	>8	128	>4	8	8	4
14	>16	256	>8	256	>4	4	<0.5	4
15	>32	128	>32	128	ND	1	0.125	2

For meropenem and ertapenem MICs, BMD was performed. Values are expressed as mg/L.
Abbreviations: MEM, meropenem; ERT, ertapenem; FQ, fluoroquinolones; COL, colistin; TIG, tigecycline; ND, not determined; BMD, Broth Macrodilution Method.

Clin Microbiol Infect 2016; 22: 147–153

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COMBINED THERAPY WITH IN VITRO SYNERGY FOR THE TREATMENT OF COLISTIN RESISTANT ENTEROBACTERIACEAE-KPC INFECTIONS

S. De Gregorio[1*], M. Nastro[2], N. Pozzi[1], C. Rodriguez[2], C. Vay[2], A. Famiglietti[2], D. Stecher[1], M. Foccoli[1]
1-Division Infectología. 2-Sección Bacteriología Hospital de Clínicas Universidad de Buenos Aires. Argentina.
*remdg@hotmail.com

Introduction and Objective

Antimicrobial treatment of KPC-producing *Enterobacteriaceae* isolates has not been well established yet. One proposed strategy is the use of combined antibiotic therapy.

Objective

To analyze the clinical outcome of patients with colistin-resistant- KPC-producing *K. pneumoniae* infection (CR-KPC-Kpi) treated with combined antimicrobial therapy with confirmed *in vitro* synergy.

Materials and Methods

Study: retrospective and observational.
Data was extracted from inpatients' medical charts with CR-KPC-Kpi (MIC ≥ 4 µg/ml, EUCAST) at a university hospital from January 2010 to October 2013.
We evaluated age, sex, focus of infection, treatment and mortality at 28 days.
Definitions of focus of infection: according to CDC criteria
In vitro synergy was evaluated by killing curves or by comparing MIC/MBC values with and without a sub-inhibitory concentration of the antimicrobial used as synergistic.

Results

Nineteen episodes of CR-KPC-Kpi were analyzed. Mean age: 57 years, 11 were men. Two patients received synergistic combination therapy and infectious focus wasn't removed and all of them died.
In next table we describe the outcome of 17 patients with adequate focus removal if necessary, and different antimicrobial treatments.
Synergistic associations were: a- colistin/rifampicin in all isolates, b- Other synergies: colistin/ piperacillin-tazobactam (1 isolate), colistin/ ciprofloxacin (1 isolate), colistin/ tigecycline (1isolate).
Fifteen patients were treated with antimicrobial combination and 33% died.
All seven patients treated with *in vitro* synergistic antibiotics associations survived. Carbapenems MIC was ≥ 64 in 6/8 patients treated with colistin/carbapenems, 3 (37%) survived (lower UTI 2 and VAP 1).

Results

Infectious focus	CST MIC (µg/ml)	Cb MIC (µg/ml)	TGC MIC (µg/ml)	FOF MIC (µg/ml)	In vitro synergy	Result	Antibiotic treatment	Mortality 28 days		Treatment
Thorax SSI	32	64	1	16	CST-RIF	S	CST	Y	100% (1/1)	Monotherapy resistant
Urological SSI	16	64	1	>64	CST-RIF	S	TGC	N	0% (0/1)	Monotherapy susceptible
Abdominal SSI	64	64	1	>64	CST-RIF	S	CST + IPM	Y	63% (5/8)	Combined therapy Colistin + carbapenem
Abdominal SSI	4	64	1	>64	CST-RIF	S	CST + IPM	Y		
Abdominal SSI	64	64	1	32	CST-RIF	S	CST + IPM	N		
VAP	>64	64	1	32	CST-RIF	S	CST + IPM	Y		
BSI	32	64	2	16	CST-RIF	S	CST + IPM + FOF + TGC	Y		
BSI	8	64	2	>64	CST-RIF	S	CST + MEM	Y		
Lower UTI	4	8	2	16	CST-RIF	S	CST + MEM	N		
Lower UTI	8	≤4	0.5	—	CST-RIF	S	CST + MEM	N		
Neurosurgical SSI	32	>16	1	8	CST - RIF CST-MEM CST-CIPX CST-TZP	S S S S	CST + RIF + TGC	N	0% (0/7)	Combined therapy with *in vitro* synergy
Abdominal SSI	8	64	6	16	CST-RIF	S	CST + RIF + MEM	N		
HAP	16	64	1	32	CST-RIF	S	CST + RIF	N		
CABSI	16	64	1	16	CST-RIF	S	CST + RIF + TGC	N		
BSI	64	16	1	—	CST-RIF CST-MEM CST-TGC	S S S	CST + RIF + MEM CST + TGC	N		
Bacteriemic UTI	8	64	2	8	CST-RIF CST-TGC	S I	CST + RIF	N		
Lower UTI	32	8	1	16	CST-RIF	S	CST + TGC CST + RIF	N		

CST: colistin, Cb: carbapenems, IPM: imipenem, MEM: meropenem, FOF: fosfomycin, TGC: tigecycline, RIF: rifampicin, TZP: Piperacillin-tazobactam, CIPX: ciprofloxacin. SSI: surgical site infection, VAP: ventilator associated pneumonia, HAP: Hospital-acquired pneumonia, UTI: urinary tract infection, BSI: bloodstream infection, CABSI: catheter associated bloodstream infection. S: susceptible, I: intermediate.

Conclusions

The best outcome was observed in patients treated with *in vitro* synergistic combined antimicrobial therapy. In this study colistin/ rifampicin was synergistic in all isolates. The removal of focus of infection was a basic requirement for survival when it was necessary.

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REVIEW

Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing *Enterobacteriaceae*

Jesús Rodríguez-Baño,[a] Belén Gutiérrez-Gutiérrez,[a] Isabel Machuca,[b] Alvaro Pascual[a]

[a]Unidad Clínica de Enfermedades Infecciosas y Microbiología, Hospital Universitario Virgen Macarena/Universidad de Sevilla/Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain
[b]Unidad Clínica de Enfermedades Infecciosas, Hospital Universitario Reina Sofía/IMIBIC, Córdoba, Spain

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)

Teşekkürler