KOLİSTİN DİRENÇLİ KLEBSİELLA SALGIN İNCELEMESİ

Dr. Şirin MENEKŞE

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

Kartal Koşuyolu Yüksek İhtisas Eğitim Araştırma Hastanesi

KOLISTIN

- Kolistin, siklik yapılı katyonik polipeptid
- 5 farklı kimyasal yapı (polimiksin A-E)
- Klinik uygulamada: polimiksin B ve E (kolistin)

  Polimiksin B, kolistinden daha toksik

- 1949 Bacillus polymyxa subspecies colistinus
- 1980'lerde ciddi nefrotoksisiteleri nedeniyle terk
- Günümüzde yeniden kullanıma

- Kolistin sülfat: oral ve tropikal
- Kolistimetat sodyum: IV formu

(Türkiye'de 2010 da ruhsat aldı)

ETKI MEKANIZMASI

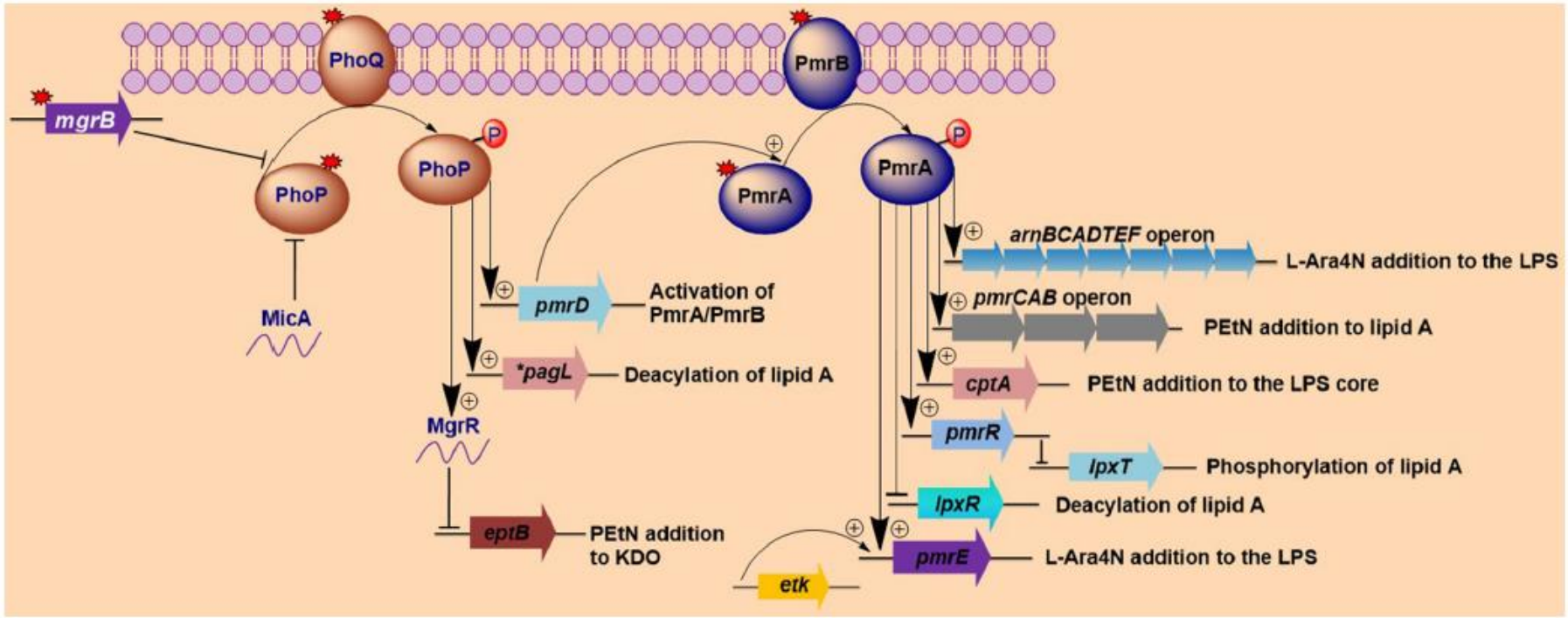
1) **Dış membranın yapısını bozar**

- Polimiksinler; kuvvetli katyonik yapıda (kuvvetli pozitif yük) ve hidrofilik aril zincire sahip
- Hedefi gram negatiflerin dış memranındaki anyonik yapıda (negatif yüklü) LPS yapıya bağlanma
- Hücrenin iki valanlı katyonları olan Ca +2 ve Mg +2 ile yer değiştirir

2) anti-endotoksin etki

- Gram negatiflerin LPS moleküllerinin Lipid A bölümüne bağlanarak endotoksin aktivitesini nötralize eder
- Bakterilerin kolistine duyarlılığı, hücre membranının içerdiği fosfolipid miktarı ve ortamda bulunan divalan katyonların düzeyi ile ilişkilidir

DİRENÇ MEKANİZMASI



Olaitan et al. Polymyxin resistance in Gram-negative bacteria

Global assessment of the antimicrobial activity of polymyxin B against 54 731 clinical isolates of Gram-negative bacilli: report from the SENTRY antimicrobial surveillance programme (2001–2004)

A. C. Gales[1], R. N. Jones[2,3] and H. S. Sader[1,2]

[1]Division of Infectious Diseases, Universidade Federal de São Paulo, São Paulo, Brazil, [2]JMI Laboratories, North Liberty, IA, USA, and [3]Tufts University School of Medicine, Boston, MA, USA

Table 2. Antimicrobial activity of polymyxin B, compared with other antimicrobial agents tested, against 40 923 isolates of Enterobacteriaceae (SENTRY antimicrobial surveillance programme, 2001–2004)

Organism/antimicrobial agent (no. tested)	MIC (mg/L)			% susceptible/ resistant[a]
	50%	90%	Range	
Klebsiella spp.[a] (8188)				
Polymyxin B	≤1	≤1	≤1–>8	98.2/1.8
Ceftriaxone	≤0.25	32	≤0.25–>32	85.5/9.7
Cefepime	≤0.12	4	≤0.12–>16	92.4/5.9
Piperacillin/tazobactam	2	64	≤0.12–>64	87.4/9.6
Imipenem	≤0.5	≤0.5	≤0.5–>8	99.7/0.2
Ciprofloxacin	≤0.03	2	≤0.03–>4	89.5/8.9
Gentamicin	≤2	>8	≤2–>8	85.9/12.8

Clin Microbiol Infect 2006; 12: 315–321

Tigecycline activity tested against carbapenem-resistant Enterobacteriaceae from 18 European nations: results from the SENTRY surveillance program (2010–2013)

Helio S. Sader *, Mariana Castanheira, Robert K. Flamm, Rodrigo E. Mendes, David J. Farrell, Ronald N. Jones

JMI Laboratories, N

Table 2
Activity of tigecycline and comparator antimicrobial agents when tested against of Enterobacteriaceae, including carbapenem-resistant strains, from European hospitals.

Antimicrobial agent	MIC_{50}	MIC_{90}	EUCAST[a] %S/%I/%R	CLSI[a] %S/%I/%R
Enterobacteriaceae (14,286)[a]				
Tigecycline[b]	0.12	0.5	98.3/1.4/0.3	99.7/0.3/<0.1
Ceftriaxone	≤0.06	>8	79.3/0.8/19.9	79.3/0.8/19.9
Ceftazidime	0.25	32	80.7/3.3/16.0	84.0/2.3/13.7
Cefepime	≤0.5	16	83.9/4.1/12.0	89.6/1.7/8.7
Imipenem	≤0.12	0.5	98.2/0.5/1.3	97.5/0.7/1.8
Meropenem	≤0.12	≤0.12	98.1/0.5/1.4	98.0/0.1/1.9
Piperacillin/tazobactam	2	64	82.2/4.5/13.3	86.7/6.1/7.2
Levofloxacin	≤0.5	>4	77.0/1.2/21.8	78.2/2.6/19.2
Amikacin	2	4	95.7/2.2/2.1	97.9/1.5/0.6
Gentamicin	≤1	≤1	87.9/0.9/11.2	88.8/0.5/10.6
Colistin	≤0.5	2	91.8/0.0/8.2	
CRE (280)[c]				
Tigecycline[b]	0.5	2	88.6/8.2/3.6	96.8/3.2/0.0
Ceftriaxone	>8	>8	0.4/0.4/99.3	0.4/0.4/99.3
Ceftazidime	>32	>32	0.0/0.7/99.3	0.7/1.1/98.2
Cefepime	>16	>16	0.7/1.4/97.9	1.1/3.2/95.7
Piperacillin/tazobactam	>64	>64	0.4/0.7/98.9	1.1/1.8/97.1
Levofloxacin	>4	>4	5.3/3.2/91.4	8.6/2.5/88.9
Amikacin	32	>32	21.4/15.7/62.9	37.1/48.2/14.6
Gentamicin	2	>8	61.8/10.4/27.9	72.1/1.4/26.4
Colistin	≤0.5	>8	73.9/0.0/26.1	

[a] Includes *C. freundii* (332 strains), *Citrobacter koseri* (300 strains), *E. aerogenes* (416 strains), *E. cloacae* (1350 strains), *E. coli* (7604 strains), *K. oxytoca* (738 strains), *K. pneumoniae* (2670 strains), and *S. marcescens* (876 strains).

[b] Criteria as published by the CLSI (CLSI, 2014) and EUCAST (EUCAST, 2014).

[c] Meropenem or imipenem MIC of ≥4 μg/mL. Includes *C. freundii* (3 strains), *E. aerogenes* (4 strains), *E. cloacae* (22 strains), *E. coli* (1 strain), *K. oxytoca* (4 strains), *K. pneumoniae* (242 strains), and *S. marcescens* (4 strains).

J Antimicrob Chemother 2015; **70**: 2133–2143
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Journal of Antimicrobial Chemotherapy

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

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- 2010-2013 yılları arasında
- Kolistin direnci % 11 den %27'e artış
- Mortalite ile ilişkili

RAPID COMMUNICATIONS

Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

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5. The network EuSCAPE-Italy participants are listed at the end of this article
6. Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, the Netherlands
7. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
8. Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Flore

- 178 KPC-KP -76 (%43) Kolistin'e dirençli
- 11 (%6) Tigesiklin'e orta duyarlı/dirençli
- 29(%16) Gentamisin'e orta duyarlı/dirençli

EuSCAPE: European Survey on Carbapenemase-producing Enterobacteriaceae; KPC: *Klebsiella pneumoniae* carbapenemase; KPC-KP: KPC-producing *K. pneumoniae*.

The peripheral laboratories are numbered on the map according to alphabetical order.

Proportions of colistin-resistant isolates among KPC-KP per peripheral laboratory:. 1, Alessandria: 1/10; 2, Ancona: 8/10; 3, Ferrara: 1/4; 4, Florence: 5/10; 5, Foggia: 4/10; 6, Lecco: 2/9; 7, Milan: 1/10; 8, Modena: 3/7; 9, Neaples: 3/8; 10, Perugia: 5/10; 11, Reggio Calabria: 4/10; 12, Rome: 4/9; 13, Rome: 2/4; 14, Rome: 6/7; 15, San Remo: 4/8; 16, Siena: 6/8; 17, Treviso: 1/7; 18, Turin: 5/9; 19, Udine: 2/8; 20, Venice: 8/10; 21, Vercelli: 1/10.

KLİMİK- Sağlık Bakımıyla İlişkili İnfeksiyonlar Çalışma Grubu

15 Merkez

Kolistin direnci:

Tüm Gram negatif bakteriler: % 3.8

Acinetobacter baumannii: % 3.2

Ergönül Ö ve ark. USBİS 2013

ORALLY ADMINISTERED COLISTIN LEADS TO COLISTIN-RESISTANT INTESTINAL FLORA AND FAILS TO PREVENT FAECAL COLONISATION WITH EXTENDED-SPECTRUM B-LACTAMASE-PRODUCING ENTEROBACTERIA IN HOSPITALISED NEWBORNS

- Nekrotizan Enterokolit Profilaksisi-Yenidoğan Yoğun Bakım
- Gentamisin 15 mg/kg/gün veya oral Kolistin 8 mg/kg/gün
- Oral kolistin alanlarda Kolistin direnci daha fazla (p=0.0075)
- Sonuç: Oral Kolistin ESBL(+) enterobactericea önlemiyor ve Kolistin direncinin seçilmesi ve indüklemesi

Strenger et al. Int J Antimicrob Agent. 2011 Jan;37(1):67-9

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

- 30 Kol-R *K.pneumoniae*
- Rep-PCR ile 20 farklı klon, 15 tanesi kolistin tedavi sırasında, diğerleri başka hastanelerden
- Kolistin **kullanım süresi** direnç gelişiminde önemli

Kontopidou et all. Clin Microbiol Infect 2011; 17: 9–11

Clinical and Molecular Factors Effecting Colistin Resistance in *Klebsiella pneumoniae*

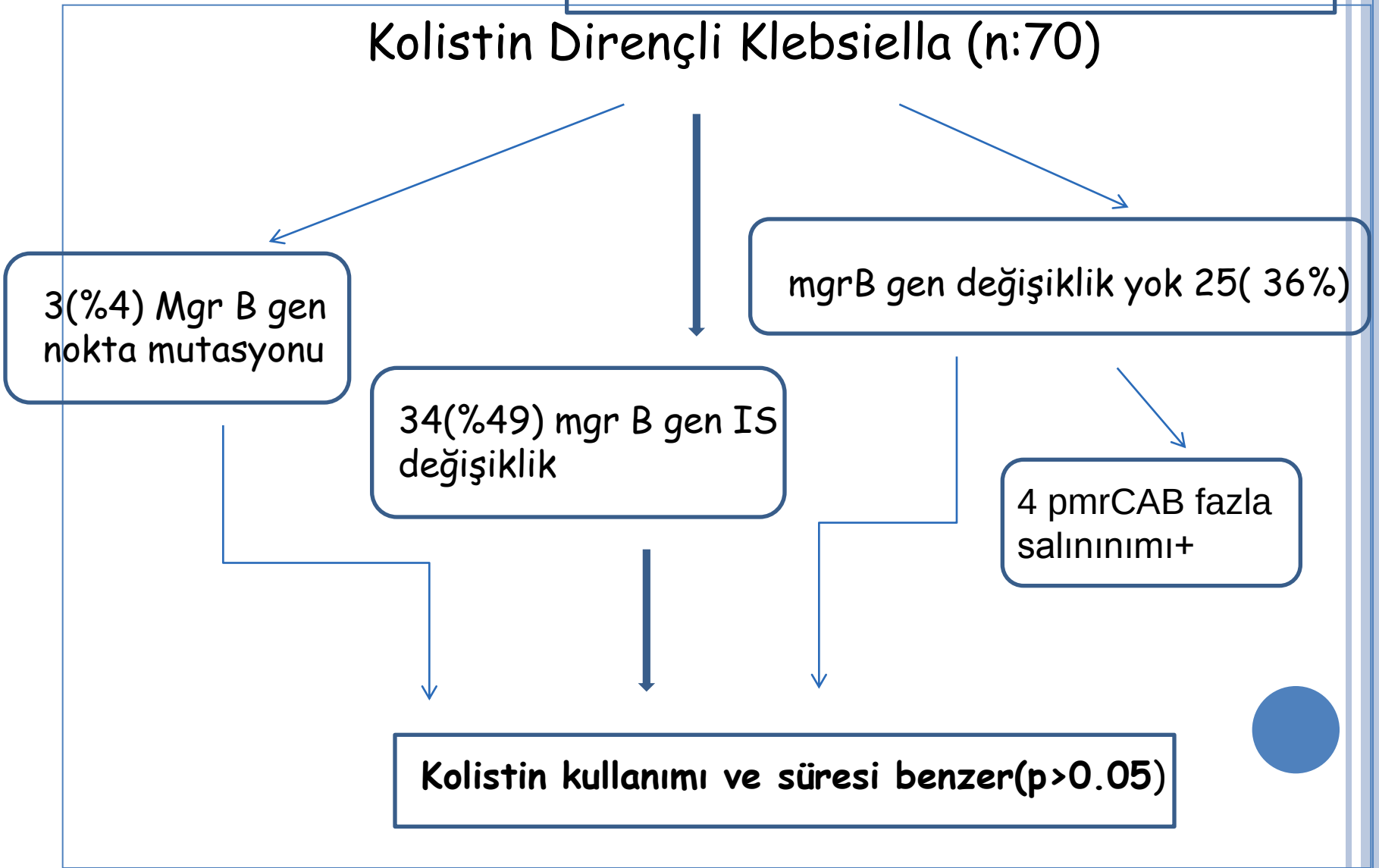
Author Block: P. Ispir[1], **F. Can**[1], S. Menekse[2], N. Lack[1], O. Azap[3], F. Timurkaynak[4], O. Ergonul[1]; [1]Koc Univ., Istanbul, Turkey, [2]Kosuyolu Training Hosp., Istanbul, Turkey, [3]Baskent Univ., Ankara, Turkey, [4]Baskent Univ., Istanbul, Turkey

- 32 Kol-R Klebsiella pneumoniae suşu
- Ortalama yaş 58 ±21
- %69 kadın cinsiyet
- %28 hasta bakteriyemi
- 22/32 kolistin kullanımı
- Mortalite %64
- %76 OXA-48 karbapenamaz
- Kolistin süresi direnç gelişiminde önemli
- MgrB gen mutasyonu dirençte daha önemli

ICCAC 2015

ÇALIŞMANIN DEVAMI

mgrB gen ve mcr 1 de değişiklik olmaması dirençte başka mekanizmalar olabilir. mgrB gen mutasyonu-- kolistin kullanımı???



Journal of Antimicrobial Chemotherapy (2007) **59**, 786–790
doi:10.1093/jac/dkl562
Advance Access publication 16 February 2007

JAC

Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multiclonal cluster

Anastasia Antoniadou[1]*, Flora Kontopidou[1], Garifalia Poulakou[1], Evangelos Koratzanis[1], Irene Galani[1], Evangelos Papadomichelakis[2], Petros Kopterides[2], Maria Souli[1], Apostolos Armaganidis[2] and Helen Giamarellou[1]

[1]*Fourth Department of Internal Medicine, Athens University Medical School, University General Hospital 'ATTIKON', Athens, Greece;* [2]*Second Department of Intensive Care, Athens University Medical School, University General Hospital 'ATTIKON', Athens, Greece*

- Atina - 750 yataklı hastane
- Kasım 2003- MDR Gr(-)hasta- Kolistin kullanımı
- İlk Kol-R Klebsiella Mayıs 2004(6 ay sonra)
- Mayıs 2004-Ağustos 2005 18 Kol-R-*K.pneumoniae* (13 hasta)

Journal of Antimicrobial Chemotherapy (2007) **59**, 786–790
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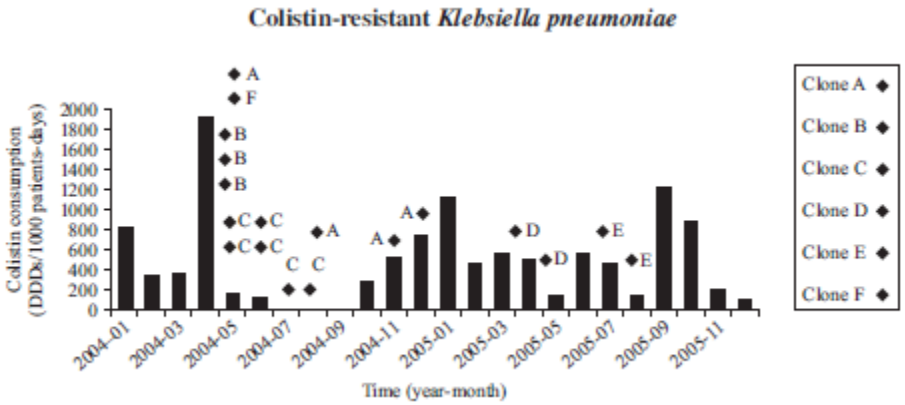
[1]*Fourth Department of Internal Medicine, Athens University Medical School, University General Hospital 'ATTIKON', Athens, Greece;* [2]*Second Department of Intensive Care, Athens University Medical School, University General Hospital 'ATTIKON', Athens, Greece*

Patient	Age	APACHE II at admission	MV	CVVH	Isolate clone	Source	ESBL	MBL	Colistin DD (mm)	Colistin MIC (mg/L)	Days in ICU at isolation	Days of colistin treatment at isolation	Colonization/ infection	Treatment for the infection	Outcome of infection	Overall outcome
1	71	32	+	+	C	BRS	+	−	12	24	63	0	colonization			good (left ICU)
2	69	38	+	−	B	BRS	−	−	10	24	24	23	colonization			
					B	faeces	+	+	9	32	28	27	colonization			
					C	blood	+	+	10	96	28	27	bacteraemia	intravenous tetracycline	cure	death from other infection
3	75	47	+	+	B	BRS	+	−	10	256	49	29	colonization			
					F	pus	+	+	10	64	53	33	STI	intravenous tetracycline	stable	death
4	84	12	+	+	C	BAL	−	+	13	96	21	4	VAP	imipenem	improvement	death from other infection and GI bleeding
5	63	18	+	+	A	BRS	+	+	15	24	13	18	colonization			death
6	57	5	+	−	C	urine	+	+	13	24	39	17	colonization			death
7	75	20	+	+	A	urine	+	+	10	64	65	45	colonization			death from
					C	pus	−	−	13	64	65	45	STI	imipenem	stable	infection with
					C	blood	+	+	7	128	65	45	bacteraemia	tigecycline	failure	colistin-resistant isolate
8	59	12	+	+	A	faeces	+	+	0	16	32	30	colonization			death
9	67	34	+	+	A	urine	+	+	12	>1024	31	30	colonization			death
10	80	18	+	+	D	faeces	+	+	12	24	24	15	colonization			good (left ICU and hospital)
11	59	11	+	−	E	BRS	−	+	14	12	115	19	colonization			death
12	76	20	+	+	D	BRS	+	−	14	16	65	28	colonization			death
13	76	18	+	−	E	BRS	+	+	0	12	48	0	colonization			death

STI, soft tissue infection; DD, disc diameter; BRS, bronchial secretions; MV, mechanical ventilation; CVVH, continuous veno-venous haemofiltration.

Using REP-PCR, 6 distinct clones (A–F) were identified among the 18 isolates (Figure 1). Clones A, B, C and F appeared concomitantly in May 2004 in three patients, as a cluster, after a peak in colistin consumption in the ICU (Figure 1). Different clones were recorded to coexist in patients (Table 1). During the following 6 months (May–November 2004), a horizontal transmission of Clone C to four patients and Clone A to three patients was recorded. Clones D and E appeared many months later (Figure 1) and were horizontally transmitted to two patients (one each). All CRKB clones vanished after the patients who harboured them either died or left the ICU.



Horizantal geçiş ve aşırı/yetersiz kolistin kullanımı

Large Nosocomial Outbreak of Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae* Traced to Clonal Expansion of an *mgrB* Deletion Mutant

Tommaso Giani,[a] Fabio Arena,[a] Guendalina Vaggelli,[b] Viola Conte,[a] Adriana Chiarelli,[a] Lucia Henrici De Angelis,[a] Rossella Fornaini,[c]

TABLE 1 Observed BSI caused by *K. pneumoniae* during the study period[a]

Yr	No. of *K. pneumoniae* BSI	No. (%) of *K. pneumoniae* isolates that were:			Colistin consumption[d]
		Carbapenemase sensitive	Carbapenemase resistant[b]	COL^r CRKP[b,c]	
2009	29	28 (97)	1 (3)	0 (0; 0)	0.004
2010	49	38 (78)	11 (22)*	1 (3; 9)	0.013
2011	76	44 (58)	32 (42)*	4 (5; 12)	0.018
2012	128	46 (36)	82 (64)*	53 (41; 65)*	0.014
2013	93	32 (34)	61 (66)	35 (38; 57)	0.015
Total	375	188 (50)	187 (50)	93 (25; 50)	

[a] Numbers and proportions of BSI cases caused by carbapenem-susceptible, carbapenem-resistant, and carbapenem- and colistin-resistant (COL^r CRKP) strains. For patients with recurrent BSI episodes, only the first episode was considered.

[b] An asterisk indicates that the difference in the proportion of resistant isolates was statistically significantly different ($P < 0.05$) from that for the previous year. For statistical analysis, the chi-squared test with Yates' correction or Fisher's exact test (as appropriate) was used.

[c] Proportions are reported in relation to both *K. pneumoniae* BSI and CRKP BSI. (Values are shown in parentheses and separated by semicolons.) COL^r *K. pneumoniae* was only observed among CRKP cases.

[d] Data on colistin consumption in the hospital during the study period, expressed as the defined daily dose per 1,000 inhabitants per day, are also reported.

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TABLE 2 Characterization of the 59 COL^r CRKP isolates investigated in this work

No. of isolates	PFGE profile[a]	ST	KPC variant	Status of *mgrB* locus[b]	Status of PmrA and PmrB[c]	Yr of isolation (*n*)
50	A	512	KPC-3	Δnt109/119 (frameshift and premature termination)	NT	2011 (1) 2012 (19) 2013 (30)
1	A	512	KPC-3	Insertional inactivation by IS*Kpn26* at nt 75 (FW)	PmrA WT PmrB WT	2013
5	A	512	KPC-3	WT	PmrA WT PmrB WT	2012 (2) 2013 (3)
2	B	101	KPC-2	WT	PmrA^{C650T} PmrB WT	2012 (1) 2013 (1)
1	C	101	KPC-2	WT	PmrA^{C650T} PmrB WT	2012 (1)

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Tommaso Giani,[a] Fabio Arena,[a] Guendalina Vaggelli,[b] Viola Conte,[a] Adriana Chiarelli,[a] Lucia Henrici De Angelis,[a] Rossella Fornaini,[c]

- 38 hastanın kolistin kullanımı bilgisine ulaşılmış.
- 35 hasta kullanmamış.
- 3 hasta (5-32 gün) kullanmış

SURVEILLANCE AND OUTBREAK REPORTS

Ongoing spread of colistin-resistant *Klebsiella pneumoniae* in different wards of an acute general hospital, Italy, June to December 2011

C Mammina (caterina.mammina@unipa.it)[1], C Bonura[1], F Di Bernardo[2], A Aleo[1], T Fasciana[1], C Sodano[2], M A Saporito[2], M S Verde[2], R Tetamo[3], D M Palma[3]

1. Department of Sciences for Health Promotion G D'Alessandro, University, Palermo, Italy
2. Laboratory of Clinical Microbiology, ARNAS General Hospital Civico, di Cristina e Benfratelli, Palermo, Italy
3. II Intensive Care Unit, ARNAS General Hospital Civico, di Cristina e Benfratelli, Palermo, Italy

- Haziran 2011-aralık 2011
- Genel yoğunbakım, plastikcerrahi kliniği,kardiyak cerrahi, beyin cerrahi, üroloji,göğüs hastalıkları yoğun bakım
- 58 Kol-R K.pneumoniae a izolatı-28 hasta
- 52 izolat bla KPC3 VE ST258, MIC:6-128 mg/L
- 6 izolat karbapenem duyarlı,ST15 ve ST273MİC:3-32 mg/L
- Kolistin kullanımı risk
- Horizantal yayılım ve secici etki

Hospital outbreak caused by *Klebsiella pneumoniae* producing KPC-2 β-lactamase resistant to colistin

- Şubat-Haziran 2008, Yunanistan, 2 hastane
- 7 hasta- 5 exitus
- **2 hastanedeki suşlar** genetik olarak ilişkili
- Bla-KPC 2, bla SHV-12

K. Kontopoulou et al. J Hospital Infect. 2010 Sep;76(1):70-3

JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2011, p. 4022–4023
0095-1137/11/$12.00 doi:10.1128/JCM.01233-11

Vol. 49, No. 11

Shudan Chen†
Fupin Hu†
Institute of Antibiotic

Independent Emergence of Colistin-Resistant *Enterobacteriaceae* Clinical Isolates without Colistin Treatment▽

- Nisan 2009-Şubat 2010
- 58CRE, 14 diğer CRE
- Kolistin duyarlılığı %92.7,Tigesiklin %85 duyarlı

TABLE 1. Laboratory and clinical characteristics of 4 colistin-resistant *Enterobacteriaceae* isolates

Species, strain	Specimen source	MIC (μg/ml)[a]					Resistance mechanism				Clinical characteristics of patients		
		MEM	ETP	IMP	CLO	TGC	Carbapenemase	ESBL(s)	Porin expression		Antibiotic therapy	Underlying disease	Outcome
									OmpK35	OmpK36			
Enterobacter cloacae													
09-1210	Urine	64	128	32	>64	1	KPC-2	CTX-M-99	Loss	Loss	None	None	Improved
Klebsiella pneumoniae													
09-1999	Sputum	2	4	16	>64	8	None	None	Loss	Decreased	Cephalosporin	None	Uncured
09-3091	Sputum	>256	>256	256	>64	1	KPC-2	SHV-12, CTX-M-15	Normal	Loss	Quinolones, aminoglycoside	None	Improved
09-3011	Sputum	32	128	32	4	2	KPC-2	SHV-12, CTX-M-99	Decreased	Loss	Carbapenem, cephalosporin, quinolones, aminoglycoside	None	Improved

Worldwide emergence of colistin resistance in *Klebsiella pneumoniae* from healthy humans and patients in Lao PDR, Thailand, Israel, Nigeria and France owing to inactivation of the PhoP/PhoQ regulator *mgrB*: an epidemiological and molecular study

- 869 gayta örneği
- Kolistin dirençli *K.Pneumonia* (MIC:2mcg/ml)
- 32 Kolistin dirençli *K.pneumonia*, 2 Kolistin Dirençli *K.oxytoca*(MDR değil)
- Kolistin direnci Laos'da %5.8 Tayland'da %6.6 Nijerya'da %0.7 Fransa'da %2.4

Bu 34 suşun 29 u CSKP ile de kolonize

A.O. Olaitan et al. / International Journal of Antimicrobial Agents 44 (2014) 500–507

Worldwide emergence of colistin resistance in *Klebsiella pneumoniae* from healthy humans and patients in Lao PDR, Thailand, Israel, Nigeria and France owing to inactivation of the PhoP/PhoQ regulator *mgrB*: an epidemiological and molecular study

and *Klebsiella oxytoca* strains.

Antimicrobial agent	Laos ($n = 11$)	Thailand ($n = 14$)	France ($n = 8$)	Nigeria ($n = 1$)
AMC	90.1	92.9	100.0	0.0
CRO	100.0	100.0	100.0	100.0
CTX	100.0	100.0	100.0	100.0
ATM	100.0	100.0	100.0	100.0
FOX	100.0	100.0	100.0	100.0
TIM	100.0	92.9	100.0	100.0
IPM	100.0	100.0	100.0	100.0
TOB	100.0	85.7	87.5	0.0
GEN	100.0	92.9	87.5	100.0
AMK	100.0	78.6	100.0	0.0
KAN	100.0	100.0	100.0	100.0
CIP	63.6	92.9	100.0	0.0
OFX	100.0	100.0	100.0	100.0
SXT	54.5	85.7	75.0	0.0
COL	0.0	0.0	0.0	0.0

AMC, amoxicillin/clavulanic acid; CRO, ceftriaxone; CTX, cefotaxime; ATM, aztreonam; FOX, cefoxitin; TIM, ticarcillin/clavulanic acid; IPM, imipenem; TOB, tobramycin; GEN, gentamicin; AMK, amikacin; KAN, kanamycin; CIP, ciprofloxacin; OFX, ofloxacin; SXT, trimethoprim/sulfamethoxazole; COL, colistin.

Table 1
Genetic features of *mgrB* of the isolated colistin-resistant *Klebsiella* strains.

Laos				Thailand			
Isolate	COL MIC (mg/L)	ST	*mgrB*[a]	Isolate	COL MIC (mg/L)	ST	*mgrB*[a]
KP_LH102	8	87	Intact	KP_TH20	32	1313	IS[1]
KP_LH12	32	507	Stop	KP_TH224	4	1314	Intact
KP_LH131	32	1319	Stop	KP_TH28	8	1311	IS[2]
KP_LH140	16	483	Intact	KP_TH196	8	477	IS[1]
KP_LH17	12	37	Intact	KP_TH54	16	1312	Intact
KP_LH61	24	491	Sub	KP_TH68	64	37	Intact
KP_LH70	12	2	Intact	KP_TH205	64	37	Intact
KP_LH74	12	491	Sub	KP_TH34	24	1320	Intact
KP_LH92	12	39	Intact	KP_TH166	3	661	Intact
KP_LH94	16	39	Intact	KP_TH176	12	477	IS[1]
KP_LH375	12	1315	Intact	KP_TH21	12	1308	Intact
				KP_TH213	12	37	IS[3]
				KP_TH114	8	1321	Intact
				KP_TH164	6	873	Intact

France				Nigeria			
Isolate	COL MIC (mg/L)	ST	*mgrB*[a]	Isolate	COL MIC (mg/L)	ST	*mgrB*[a]
KP_FHM120[b]	64	104	ND	KP_NH53	4	1309	Sub
KP_FHM128	4	1310	Intact				
KP_FHM169[b]	8	104	Stop				
KP_FHM77	8	13	Intact				
KP_FHA105	24	1308	ND				
KP_FHA60	8	1307	Intact				
KOX_FHA41	12	–	IS[1]				
KOX_FHA124	6	–	Intact				

Worldwide emergence of colistin resistance in *Klebsiella pneumoniae* from healthy humans and patients in Lao PDR, Thailand, Israel, Nigeria and France owing to inactivation of the PhoP/PhoQ regulator *mgrB*: an epidemiological and molecular study

SONUÇ

- Kümes ve diğer hayvanlardan Kolistin direnç

  horizantal geçiş

- Çapraz direnç ??Polimixinler-konak katyonik

  peptitler (lizozim vb)

Parisi *et al. BMC Infectious Diseases* (2015) 15:244
DOI 10.1186/s12879-015-0996-7

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Prevalence of Klebsiella pneumoniae strains producing carbapenemases and increase of resistance to colistin in an Italian teaching hospital from January 2012 To December 2014

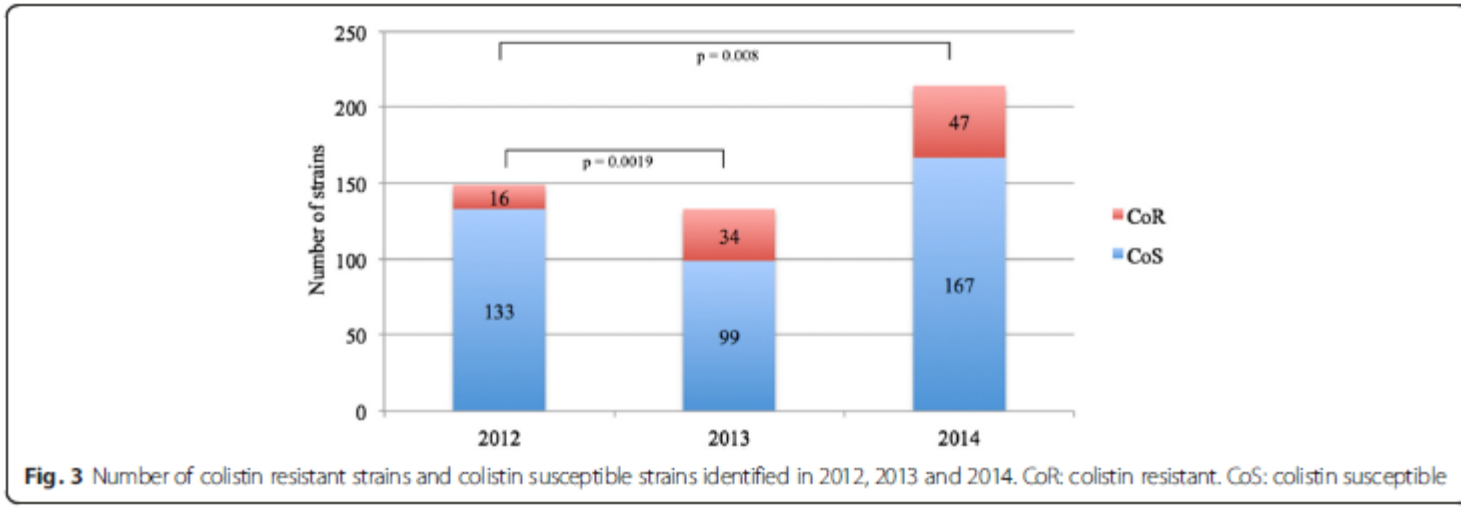


Fig. 3 Number of colistin resistant strains and colistin susceptible strains identified in 2012, 2013 and 2014. CoR: colistin resistant. CoS: colistin susceptible

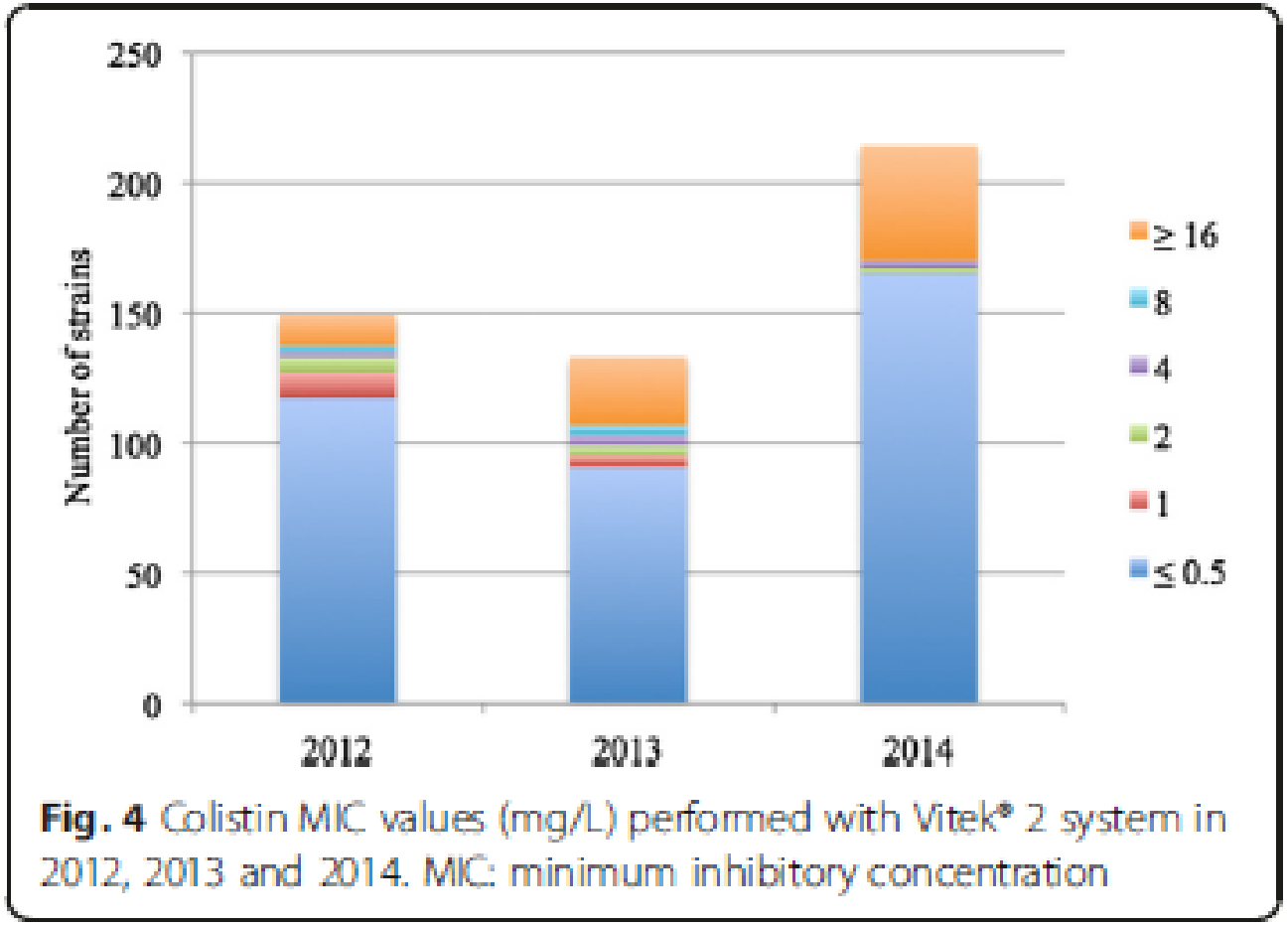


Fig. 4 Colistin MIC values (mg/L) performed with Vitek® 2 system in 2012, 2013 and 2014. MIC: minimum inhibitory concentration

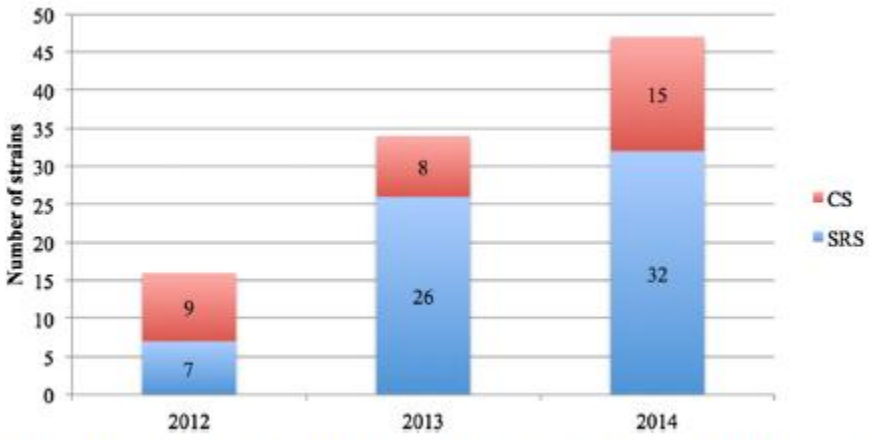


Fig. 5 Colistin resistant strains at the first detection in 2012, 2013 and 2014. CS: clinical samples. SRS: surveillance rectal samples

Colistin-Resistant *Klebsiella pneumoniae*: Report of a Cluster of 24 Cases from a New Oncology Center in Eastern India

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2014, VOL. 35, NO. 8

- Haziran 2013-Şubat 2014-Hindistan
- Farklı servislerden gelen hastalar (Gastoenterolojik cerrahi,Beyin Cerrahisi,Jinekoloji,Üroloji, Onkoloji ve Hematoloji)
- %62 hasta kolistin kullanımı
- %25 mortalite
- 15 infeksiyon-3 kolonizasyon
- 20(%83.3)sağlık bakım ilişkili infeksiyon
- Sürveyans kültürleri başlangıçta ve haftalık peryotlarla

Takip edilen 210 hastanın 50 'de kolistin duyarlı ve dirençli Klebsiella

Table 4 Longitudinal analysis of colistin susceptibility evolution in patients with a colistin susceptible isolate at the first detection in 2012, 2013 and 2014

Year	CoS at first detection (n)	Patients with FU available (n)	CoS at FU (n)	CoR at FU (n,%)
2012	133	71	59	12 (16.9 %)
2013	99	57	39	18 (31.6 %)
2014	167	82	62	20 (24.4 %)

CoS Colistin susceptible, *CoR* Colistin resistant, *FU* follow-up

4 hastada klonal farklılık(CoS ve CoR)

Table 5 MLST analysis on pairs of CoS and CoR strains obtained from the same patient. Time to switch is intended as the time-interval between the first CoS strain isolated from a clinical sample and the first CoR strain isolated from the same patient

	Strains with Stable ST					
Patient	ST of the first CoS strain isolated	Sample type	Sample type of first clinical CoS	ST of CoR strain isolated	Sample type	Time to switch from CoR to CoS (days)
1	554	SRS	Arterial catheter	-	bronchial aspirate	36
2	512	SRS	skin swab	-	urine	26
3	307	SRS	skin swab	-	skin swab	42
4	512	SRS	skin swab	-	SRS	123
5	512	SRS	drainage fluid	-	drainage fluid	28
6	512	urine	urine	-	urine	17
7	512	SRS	bronchial aspirate	-	SRS	74
8	1543	SRS	-	-	SRS	50
9	512	SRS	bronchial aspirate	-	bronchial aspirate	31
10	512	SRS	bronchial aspirate	-	bronchial aspirate	6
11	554	SRS	-	-	bronchial aspirate	na
12	512	SRS	bronchial aspirate	-	blood	24
13	258	SRS	urine	-	urine	8
						Median 29.5 days
	Switched ST					
Patient	ST of the first CoS strain isolated	Sample type	Sample type of first clinical CoS	ST of CoR strain isolated	Sample type	Time to switch from CoR to CoS (days)
14	15	SRS	urine	512	SRS	167
15	554	urine	urine	512	SRS	67
16	258[1]	SRS	skin swab	512	SRS	34
17	554	SRS	arterial catheter	1733 (554 SLV)	drainage fluid	54
						Median: 60.5 days

[1] simultaneous isolation of a ST258 CoS strains and a ST512 CoR strain from the same sample at the first detection*

CoR colistin resistant, *CoS* colistin susceptible, *MLST* Multilocus sequence typing, *na* not applicable, *SLV* single locus variant, *SRS* surveillance rectal swab, *ST* sequence typing

New Microbiologica, 38, 417-421, 2015

Containment of carbapenem resistance rates of *Klebsiella pneumoniae* and *Acinetobacter baumannii* in a Greek hospital with a concomitant increase in colistin, gentamicin and tigecycline resistance

Georgios Meletis, Efstathios Oustas, Christina Botziori, Eleni Kakasi, Asimoula Koteli

Department of Clinical Microbiology, St. Paul General Hospital of Thessaloniki, Greece

- Prokroustes Planı 2010
- Amaç: Karbapenem dirençli Klebsiella
- Sürveyans (Karbapenem dirençli) ve infeksiyon Kontrol Önlemleri

TABLE 1 - *Resistance rates of clinical isolates to carbapenems, colistin, tigecycline and gentamicin for the two study periods.*

Species	*Resistance rates to*	*Isolated from*	*Period 2007-2010*	*Period 2010-2013*	*p*
K. pneumoniae	Carbapenems	ICU patients	21/35 (60%)	92/157 (58.59%)	0.879
		Non-ICU patients	24/75 (32%)	60/189 (31.70%)	0.968
	Colistin (among CR isolates)	ICU patients	0/21 (0%)	20/92 (21.73%)	0.022
		Non-ICU patients	0/24 (0%)	5/60 (8.33%)	0.315
	Tigecycline (among CR isolates)	ICU patients	0/15 (0%)	30/92 (32.60%)	0.010
		Non-ICU patients	0/16 (0%)	18/60 (30%)	0.009
	Gentamicin (among CR isolates)	ICU patients	4/21 (19.04%)	29/92 (31.52%)	0.257
		Non-ICU patients	2/24 (8.33%)	10/60 (16.66%)	0.495
A. baumannii	Carbapenems	ICU patients	90/100 (90%)	132/156 (84.61%)	0.216
		Non-ICU patients	50/66 (75.75%)	75/114 (65.78%)	0.162
	Colistin (among CR isolates)	ICU patients	0/90 (0%)	0/132 (0%)	NA
		Non-ICU patients	0/50 (0%)	0/75 (0%)	NA
	Gentamicin (among CR isolates)	ICU patients	56/90 (62.22%)	117/132 (88.63%)	<0.001
		Non-ICU patients	34/50 (68%)	66/75 (88%)	0.006
P. aeruginosa	Carbapenems	ICU patients	18/47 (37.50%)	88/156 (56.41%)	0.022
		Non-ICU patients	22/123 (17.88%)	36/149 (24.16%)	0.209
	Colistin (among CR isolates)	ICU patients	1/18 (5.55%)	2/88 (2.27%)	0.444
		Non-ICU patients	1/22 (4.54%)	0/36 (0%)	0.197
	Gentamicin (among CR isolates)	ICU patients	11/18 (61.11%)	50/88 (56.81%)	0.737
		Non-ICU patients	16/22 (72.72%)	25/36 (69.44%)	0.790

CR: carbapenem-resistant; ICU: intensive care unit; NA: not applicable.

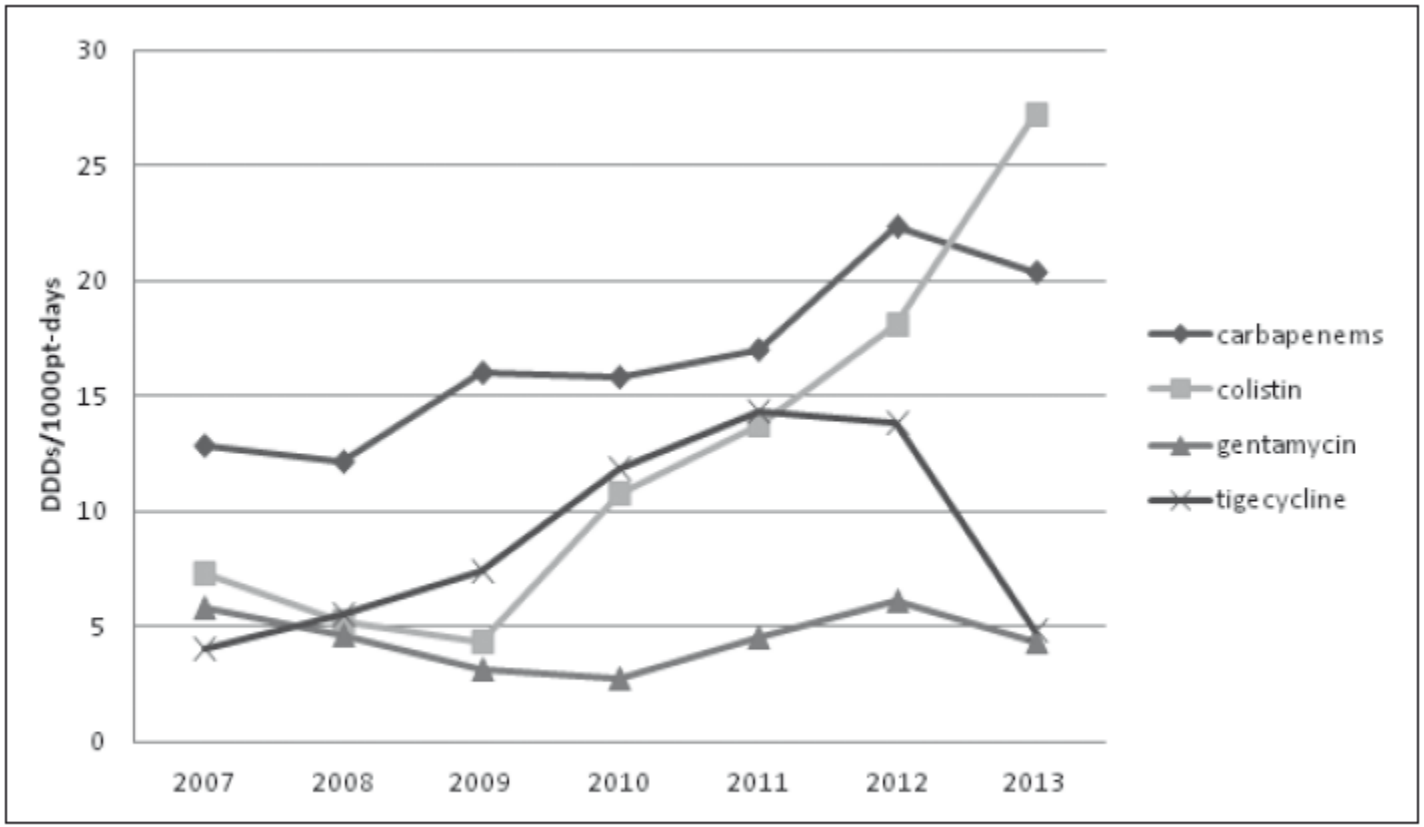


FIGURE 2 - *Trends of carbapenems, colistin, gentamicin and tigecycline defined daily doses (DDD) from 2007 to 2013.*

BMC Infectious Diseases

BioMed Central

Research article

Open Access

Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria

Matthew E Falagas*[1,2,3], Ioannis A Bliziotis[3], Sofia K Kasiakou[3], George Samonis[4], Panayiota Athanassopoulou[3] and Argyris Michalopoulos[5]

1 Ekim 2000-31 Ağustos 2004

Kol -R olgu serisi 7 hasta - 2 K.pneumoniae

2 hasta exitus

Çok da korkutucu değil!!!!!

BMC Infectious Diseases 2005, **5**:24

Risk factors for infection and predictors of mortality among patients with KPC-producing Klebsiella pneumoniae bloodstream infections in the intensive care unit

MATTHAIOS PAPADIMITRIOU-OLIVGERIS[1], MARKOS MARANGOS[1], MYRTO CHRISTOFIDOU[2], FOTINI FLIGOU[3], CHRISTINA BARTZAVALI[2], ELEFTHERIA S. PANTELI[3], SOPHIA VAMVAKOPOULOU[2], KRITON S. FILOS[3] & EVANGELOS D. ANASTASSIOU[1]

From the [1]Department of Microbiology, Internal Medicine, [2]Department of Microbiology, and [3]Anaesthesiology and Critical Care Medicine, School of Medicine, University of Patras, Greece

- 23 aylık peryot-Yunanistan
- 53 KPC-KP kan dolaşımı enfeksiyonu

  (5 gelişten enfekte)
- **%54.7** (27) Kolistin dirençli
- **Kolistin direnci –mortalite** (P<0.005)

Scandinavian Journal of Infectious Diseases, 2014; 46: 642–648

ORIGINAL ARTICLE BACTERIOLOGY

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

Clin Microbiol Infect 2013; **19:** E23–E30

A. Capone[1], M. Giannella[1], D. Fortini[2], A. Giordano[3], M. Meledandri[4], M. Ballardini[4], M. Venditti[5], E. Bordi[6], D. Capozzi[7], M. P. Balice[8], A. Tarasi[9], G. Parisi[10], A. Lappa[10], A. Carattoli[2], N. Petrosillo[1] and on behalf of the SEERBIO-GRAB network[†]

1) *2nd Division of Infectious Diseases, National Institute for Infectious Diseases "Lazzaro Spallanzani", Rome, Italy,* 2) *Department of Infectious, Parasitic and Immune-mediated Diseases, Istituto Superiore di Sanità, Rome, Italy,* 3) *Department of Microbiology, University "La Sapienza" Policlinico Umberto I, Rome, Italy,* 4) *Department of Microbiology, Azienda Ospedaliera San Filippo Neri, Rome, Italy,* 5) *Department of Infectious Diseases, University "La Sapienza" Policlinico Umberto I, Rome, Italy,* 6) *Department of Microbiology, National Institute for Infectious Diseases "Lazzaro Spallanzani", Rome, Italy,* 7) *Department of Microbiology, Azienda Ospedaliera Grassi Ostia, Rome, Italy,* 8) *Department of Microbiology, Santa Lucia Fundation, Rome, Italy,* 9) *Health-care Infectious Unit, Azienda Ospedaliera San Giovanni Addolorata, and* 10) *Microbiology and Heart Surgery ICU, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy*

MIC value (mg/L)	Strains from colonized patients *n* = 6 *n* (%)	Strains from infected patients *n* = 91, *n* (%)	Total *n* = 97, *n* (%)
0.38	0	1 (1.1)	1 (1)
0.50	3 (50)	58 (63.7)	61 (62.9)
1.00	0	1 (1.1)	1 (1)
2.00	0	1 (1.1)	1 (1)
8.00	0	1 (1.1)	1 (1)
16.00	3 (50)	29 (31.9)	32 (33)

Prospektif -multicenter çalışma-İtalya

Aralık 2010-Mayıs 2011

Vakaların 1/3 ü kolistin dirençli

High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality

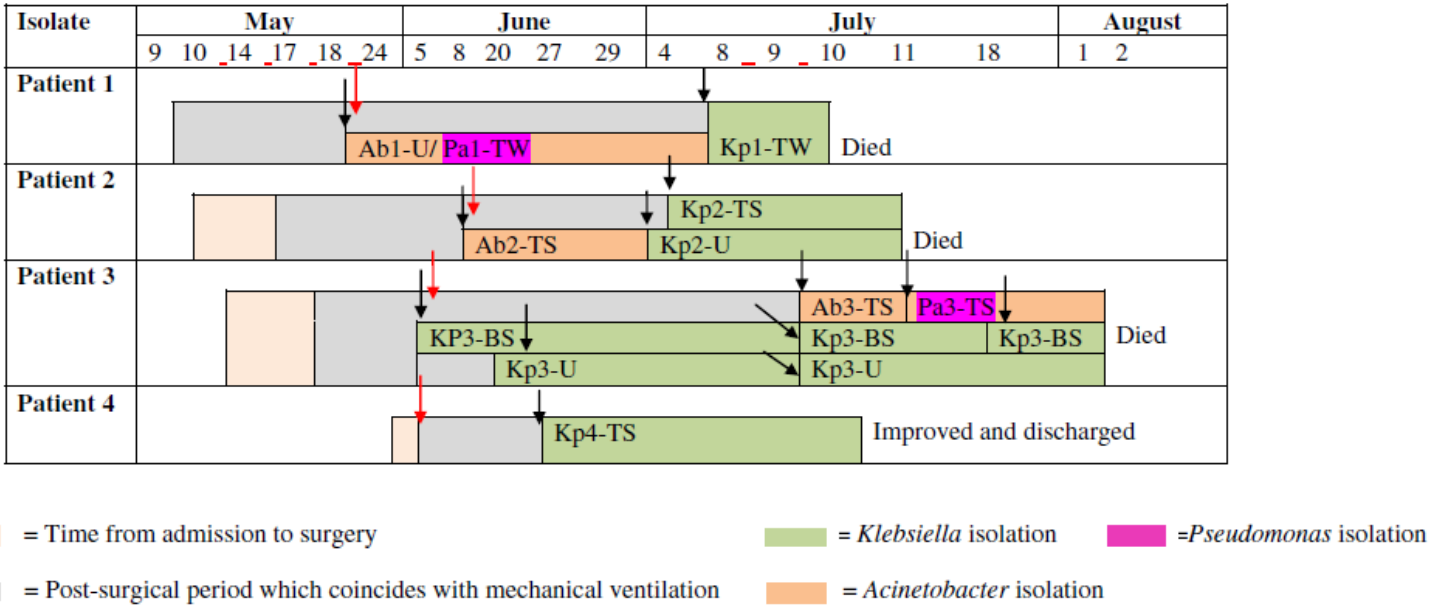
TABLE 4. Multivariate analysis of risk factors for in-hospital mortality in patients with infection due carbapenem-resistant *Klebsiella pneumoniae* (CR-KP), adjusted for appropriate antibiotic treatment, combination therapy and removal of the infectious source

	OR (95% CI)	p
Charlson comorbidity score	1.42 (1.15–1.76)	0.001
Hospitalization in intensive-care unit	18.05 (3.90–83.51)	<0.001
Bloodstream infection	4.92 (1.35–17.28)	0.01
Infection due to a colistin-resistant strain	4.15 (1.17–14.74)	0.02

Clin Microbiol Infect 2013; **19:** E23–E30

Emergence of concurrent infections with colistin-resistant ESBL-positive *Klebsiella pneumoniae* and OXA-23-producing *Acinetobacter baumannii* sensitive to colistin only in a Romanian cardiac intensive care unit

D. Timofte [1,4,5] · M. Dan [2] · I. E. Maciuca [1,4] · L. Ciucu [2] · E. R. Dabija [2] · E. Guguianu [4] · C. V. Panzaru [2,3]



An Outbreak with Colistin- and Carbapenem-Resistant *Klebsiella pneumoniae* in an Intensive Care Unit

Uluhan Sili, MD, PhD[1], Aysun Tekin, MD[1], Hüsniye Karadağ, RN[1], Gülşen Altınkanat, PhD[2], Fethi Gül, MD[3], Beliz Bilgili, MD[3], Mustafa Kemal Arslantaş, MD[3], Pınar Ay, MD, PhD[4], Güner Söyletir, MD[2], İsmail Cinel, MD, PhD[3] and Volkan Korten, MD[1]

(1) Infectious Diseases and Clinical Microbiology, Marmara University, School of Medicine, Pendik Training and Research Hospital, Istanbul, Turkey
(2) Microbiology, Marmara University, School of Medicine, Pendik Training and Research Hospital, Istanbul, Turkey
(3) Anesthesiology and Reanimation, Marmara University, School of Medicine, Pendik Training and Research Hospital, Istanbul, Turkey
(4) Public Health, Marmara University, School of Medicine, Pendik Training and Research Hospital, Istanbul, Turkey

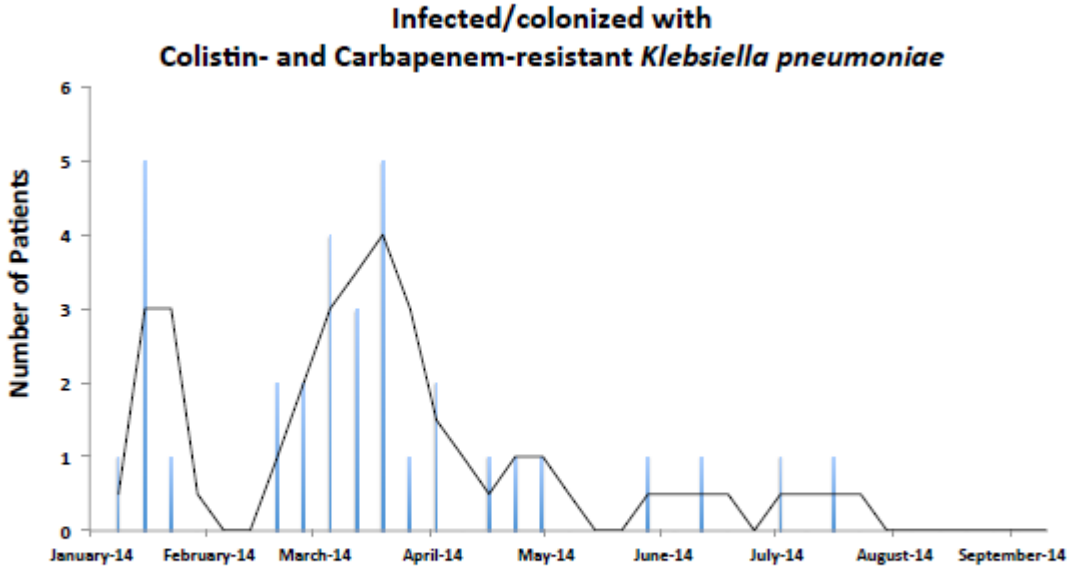


Figure 1. Colistin- and carbapenem-resistant Klebsiella pneumoniae outbreak in a 16-bed surgical intensive care unit of a university hospital.

Table 2. Comparison of colonized and infected patients with colistin-resistant CRKP

Variable	Colonized (n=16) n (%)	Infected (n=17) n (%)	*p*
Male sex	6 (37.5)	7 (41.2)	*1.000*
Age, years, median (range)	54.5 (19-89)	65 (19-80)	*0.516*
Emergency ward admission before ICU	6 (37.5)	7 (41.2)	*0.803*
Post-operative admission to ICU	7 (43.8)	5 (29.4)	*0.622*
Invasive procedure before admission to ICU	13 (81.2)	13 (76.5)	*1.000*
Admission APACHE II	19 (7-27)	21 (11-33)	*0.240*
Admission APACHE II >26	2 (12.5)	4 (23.5)	*0.656*
Charlson co-morbidity index	4 (0-7)	4 (0-7)	*0.798*
Co-colonization	14 (87.5)	15 (88.2)	*1.000*
Co-colonization with another gram negative bacilli	12 (75)	12 (70.6)	*1.000*
Central venous catheter	13 (81.2)	14 (87.5)	*0.526*
Invasive mechanical ventilation	14 (87.5)	14 (87.5)	*0.627*
Urinary catheter	16 (100)	17 (100)	*0.404*
Central venous catheter, days, median (range)	16 (4-35)	10 (0-32)	*0.526*
Invasive mechanical ventilation, days, median (range)	19.5 (3-38)	20 (1-36)	*0.627*
Urinary catheter, days, median (range)	19.5 (3-31)	21 (1-36)	*0.404*
Colistin, MIC (mg/L), median (range)	16 (8-16)	4 (3-16)	***<0.001***
Antibiotic usage before colonization/ infection	15 (93.8)	17 (100)	*0.485*
Carbapenem usage before colonization/ infection	8 (53.3)	10 (58.8)	*1.000*
Colistin usage before colonization/ infection	4 (26.7)	5 (29.4)	*1.000*
14-day fatality	6 (37.5)	6 (35.3)	*1.000*
28-day fatality	10 (62.5)	9 (52.9)	*0.728*
Overall fatality	10 (62.5)	14 (82.4)	*0.259*
Fatality post-colonization/ infection detection, days, median (range)	9 (0-22)	17 (2-236)	*0.095*

An Outbreak with Colistin- and Carbapenem-Resistant *Klebsiella pneumoniae* in an Intensive Care Unit

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(4) Public Health, Marmara University, School of Medicine, Pendik Training and Research Hospital, Istanbul, Turkey

- 2 farklı klon identifiye
- Önceki Karbapenem kullanımı mortalite için risk faktörü(p:0.015)

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
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
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	

Kontopidou et all , Colonization and infection by colistin-resistant Gram-negative bacteria, in a cohort of critically ill patients, Clin Microbiol Infect 2011; 17: 9–11

RİSK FAKTÖRLERİ

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

Clin Microbiol Infect 2015; 21: 1106.e1–1106.e8

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)

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
Solid organ cancer	26 (18.3)	65 (22.9)	0.75 (0.43–1.28)	0.28	50 (17.6)	1.05 (0.59–1.82)	0.86
Hematologic cancer	26 (18.3)	25 (8.8)	2.32 (1.23–4.38)	0.004	43 (15.1)	1.26 (0.70–2.21)	0.40
Diabetes mellitus	30 (21.1)	54 (19.0)	1.14 (0.66–1.93)	0.60	71 (25.0)	0.80 (0.48–1.33)	0.37
Splenectomy	2 (1.4)	3 (1.1)	1.34 (0.11–11.81)	0.75	4 (1.4)	1 (0.09–7.07)	1.00
Chronic renal failure	23 (16.2)	35 (12.3)	1.37 (0.74–2.51)	0.27	54 (19.0)	0.82 (0.46–1.44)	0.48
Liver disease	13 (9.1)	14 (4.9)	1.94 (0.81–4.59)	0.09	27 (9.5)	0.96 (0.44–2.00)	0.91
HIV infection	3 (2.1)	3 (1.1)	2.02 (0.27–15.26)	0.38	13 (4.6)	0.45 (0.08–1.68)	0.21
Solid organ transplantation	13 (9.1)	5 (1.8)	5.62 (1.82–20.49)	<0.001	21 (7.4)	1.26 (0.56–2.74)	0.53

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

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

TABLE 3. Characteristics of 426 patients with BSI caused by KPC-Kp according to colistin resistance (ColR) or colistin susceptibility (ColS) of the isolates

Variable	ColR patients, case group (n = 142)	ColS patients, control group B (n = 284)	p
Postantibiogram therapy			
Colistin-including therapy	14 (9.8)	208 (73.2)	<0.001
Tigecycline-including therapy	79 (55.6)	145 (51.1)	0.37
Gentamicin-including therapy	66 (46.5)	77 (27.1)	<0.001
Monotherapy	47 (33.1)	53 (18.6)	<0.001
Combination therapy	95 (66.9)	231 (81.3)	<0.001
Two-drug combinations	36 (25.3)	78 (27.5)	0.64
Three-drug combinations	49 (34.5)	151 (53.2)	<0.001
Four drug combinations	10 (7.1)	2 (0.7)	<0.001
Carbapenem-excluding combinations	28 (19.7)	72 (25.4)	0.19
Carbapenem-including combinations	67 (47.2)	159 (55.9)	0.08
Double-carbapenem combinations	15 (10.6)	6 (2.1)	<0.001
Rifampin addition to combinations	11 (7.7)	2 (0.7)	<0.001
Outcome parameters			
Initial treatment failure	38 (26.7)	42 (14.8)	0.003
Death	73 (51.4)	112 (39.4)	0.02
Time to discharge (days), median (IQR)[a]	27 (18–40)	20 (14–37)	0.04

TABLE 3. Characteristics of 426 patients with BSI caused by KPC-Kp according to colistin resistance (ColR) or colistin susceptibility (ColS) of the isolates

Variable	ColR patients, case group (n = 142)	ColS patients, control group B (n = 284)	p
Type of infection			
HCA infection	13 (9.1)	27 (9.5)	0.96
Hospital-acquired infection	129 (90.8)	257 (90.5)	0.91
Septic shock	29 (20.4)	53 (18.7)	0.66
Pitt bacteremia score ≥ 4	53 (37.3)	82 (28.8)	0.07
Source of infection			
Urinary tract	25 (17.6)	69 (24.3)	0.12
Lower Respiratory tract	29 (20.4)	34 (11.9)	0.02
Pancreas and biliary tract	3 (2.1)	8 (2.8)	0.66
Central venous catheter	36 (25.3)	62 (21.8)	0.41
Surgical wound	13 (9.1)	28 (9.9)	0.82
Other	5 (3.5)	11 (3.9)	0.86
Unknown	40 (28.2)	89 (31.3)	0.50
Inadequate empirical antimicrobial treatment	94 (66.2)	155 (54.6)	0.02

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

- Kolistin direncinde önceki kolistin kullanımı ve önceki KPC kolonizasyonu (%72 olgunun kolisitn kullnım öyküsü yok) rol oynar

- Kolistin kullanımının kısıtlanması ve mümkün olduğunca erken sonlandırılması

Infection (2014) 42:883–890
DOI 10.1007/s15010-014-0653-x

CLINICAL AND EPIDEMIOLOGICAL STUDY

The role of colonization pressure in the dissemination of colistin or tigecycline resistant KPC-producing *Klebsiella pneumoniae* in critically ill patients

M. Papadimitriou-Olivgeris · M. Christofidou ·

- Prospektif, gözlemsel çalışma
- Rektal sürüntü- kromojen agar
- 254 hastanın %24.4(62)'ü Kol-R K.pneumonia
- %17.9(39)'u Tigesiklin-R K.pneumonia ile kolonize oluyor.

Infection (2014) 42:883–890
DOI 10.1007/s15010-014-0653-x

CLINICAL AND EPIDEMIOLOGICAL STUDY

The role of colonization pressure in the dissemination of colistin or tigecycline resistant KPC-producing *Klebsiella pneumoniae* in critically ill patients

M. Papadimitriou-Olivgeris · M. Christofidou ·

Kol-R K.pneumonia Risk Faktörleri

- Steroid kullanım öyküsü
- Kolistin kullanım öyküsü
- Kol-R K.pneumoniaeiella hasta ile yakın yatakta yatış günü

Infection (2014) 42:883–890
DOI 10.1007/s15010-014-0653-x

CLINICAL AND EPIDEMIOLOGICAL STUDY

The role of colonization pressure in the dissemination of colistin or tigecycline resistant KPC-producing *Klebsiella pneumoniae* in critically ill patients

M. Papadimitriou-Olivgeris · M. Christofidou ·

Tigesiklin Dienci Risk Faktörleri:

- Obesite
- Tigesiklin kullanım öyküsü
- Tigesiklin-R Klebsiella hasta ile yakın yatakta yatış günü

Table 3 Association of pulse field gel electrophoresis (PFGE) type with resistance to antibiotics

	All isolates ($n = 57$)	PFGE type A ($n = 38$)	PFGE type B ($n = 19$)	*P*
Imipenem resistance	53 (93.0 %)	35 (92.1 %)	18 (94.7 %)	1.000
Number of antibiotic resistance	1.4 ± 1.2	0.9 ± 1.1	2.5 ± 0.5	<0.001
Colistin resistance	28 (49.1 %)	9 (23.7 %)	19 (100 %)	<0.001
Tigecycline resistance	24 (42.1 %)	13 (34.2 %)	11 (57.9 %)	0.099
Gentamicin resistance	29 (50.9 %)	12 (31.6 %)	17 (89.5 %)	<0.001

TEDAVİ

KOMBİNASYON TEDAVİ

Tekrarlayan Karbapenem Dirençli Klebsiella suşları

12 hasta Kolistin

4 hasta Kolistin +Tigesiklin

TABLE 1. Increased MIC of polymyxin B for CRKP isolates from three patients treated with polymyxin B

Isolate source	Sample type	Date of isolation (mo/day/yr)	Duration of treatment (days)	Polymyxin B MIC (μg/ml)
Patient 1	Peritoneal fluid	3/28/2006	14	1.5
	Blood	4/13/2006		32
Patient 2[a]	CSF[b]	11/5/2005	21[c]	0.75
	Blood	11/26/2005		12
Patient 3	Blood	12/7/2005	5	0.75
	Blood	12/12/2005		1,024

Jooyun Lee et all. Decreased Susceptibility to Polymyxin B During Treatment for Carbapenem-Resistant Klebsiella Pneumoniae Infection. Journal of Clinical Microbiology,2009:1611-12

Journal of Antimicrobial Chemotherapy Advance Access published March 19, 2014

J Antimicrob Chemother
doi:10.1093/jac/dku065

Journal of Antimicrobial Chemotherapy

In vitro activity and post-antibiotic effects of colistin in combination with other antimicrobials against colistin-resistant KPC-producing *Klebsiella pneumoniae* bloodstream isolates

Paolo Gaibani[1]*, Donatella Lombardo[1], Russell E. Lewis[2], Marcella Mercuri[1], Sonia Bonora[1], Maria Paola Landini[1] and Simone Ambretti[1]

- Kolistin + Rifampisin kombinasyonu +tigesiklin
- Sonuç: Sinerji ve post antibiyotik etkinin uzaması

  Heterorezistan suşların azalması

Mayıs 2013-Temmuz 2014

Travma, yanık ve böbrek nakil servisi

KPC2

30 günlük mortalite %28.6

n	Gender	Age (years)	Charlson Index	Days before BSI	Active drug (<24 h)		Active drug (<48 h)		COL MIC	AK MIC	CIP MIC	MEM MIC	Outcome
1	male	63	0	40	no	POL+VAN+TZP	no	POL+MEM+CAZ+LNZ	≥16	≥64	≥4	≥16	survival
2	male	65	0	41	yes	POL+**AK**[a]	yes	POL+**AK**[a]	≥16	≤2(S)	≥4	≥16	death
3	male	28	0	11	no	MEM+POL	no	MEM+POL	≥16	≥64	≥4	≥16	survival
4	male	66	5	24	no	MEM+TGC+POL+AK	no	MEM+TGC+POL+AK	≥16	≥64	≥4	≥16	death
5	male	40	0	17	no	MEM+VAN	no	MEM+VAN	≥16	≥64	≥4	≥16	survival
6	female	36	3	2	no	CAZ+VAN	yes	**CIP**[a]	≥16	≤2(S)	≤0.25(S)	≤0.25(S)	survival
7	male	37	0	43	no	None	no	None	≥16	≥64	≥4	≥16	death
8	female	36	6	1	no	LNZ+MEM+POL	no	MEM+POL	≥16	≤2(S)	≥4	≥16	survival
9	male	45	0	13	no	MEM	no	MEM+POL+TGC	≥16	≥64	≥4	≥16	survival
10	female	42	0	10	no	MEM+POL+TGC	no	MEM+POL+TGC+ERT	≥16	≥64	≥4	≥16	death
11	male	46	0	13	no	TGC	no	TGC	≥16	≤2(S)	≥4	≥16	survival
12	female	49	0	0	no	CRO+MTZ	yes	**AK**[a]	≥16	≤2(S)	≥4	≥16	survival
13	female	50	0	15	no	POL+TGC+MEM+AK	no	POL+TGC+MEM+AK	≥16	≥64	≥4	≥16	survival
14	female	30	0	11	no	MEM+VAN	no	POL+VAN	≥16	≥64	≥4	≥16	survival

Tuon et al.Colistin-resistant Enterobacteriaceae bacteraemia: real-life challenges and options. Clin Microbiol Infect 2015; 1–2

Infection with Panresistant *Klebsiella pneumoniae*: A Report of 2 Cases and a Brief Review of the Literature

Olgu 1: 70yaşında kadın hasta, üriner sistem infeksiyonu

- Tigesiklin+ Rifampisin(allerjik reaksiyon)
- Yeni kültürde tigesiklin MIC:8 mg/mL(eski sonuç 4mg/dl),KPC
- 10 gün tedavi-Taburculuk sonrası 1 yıl kültür pozitif

Olgu 2: 67 yaşında erkek hasta, karaciğer absesi

- Kolistin +Tigesiklin
- Karaciğer abse:*E. cloacae, K. pneumoniae, Enterococcus faecium*
- *Kan kültürleri K. Pneumoniae(kolistin dirençli)* (KPC)
- *14.günde exitus-septik şok*

Elemam et all.Clinical Infectious Diseases 2009; 49:271–4

Successful treatment of pan-resistant *Klebsiella pneumoniae* pneumonia and bacteraemia with a combination of high-dose tigecycline and colistin

Romney M. Humphries,[1] Theodoros Kelesidis,[2] Jennifer Dien Bard,[1] Kevin W. Ward,[3] Debika Bhattacharya[2] and Michael A. Lewinski[1]

- 75 yaşında, H1N1 İnfluenza –entübasyon gerekliliği
- Hastane Kaynaklı Pnömoni-27.günde-K.pneumonia-KPC 2
- **İmipenem 4x500 mg uzun infüzyon (59gün) + Tigesiklin 2x50 mg(28gün)+Minosiklin 2x200 mg PO(59gün)**
- Transfer-kan ve solunum sekresyonu-K.pneumonia
- **Kolistin 350 mg/gün IV+ İnhaler 2x75 mg ve Tigesiklin 200mg/gün+ Amikasin 2x500 mg 10 gün**
- 75.günde bakteriyemi görülmüyor.
- 95.günde transfer-kolonize

BMC Infectious Diseases

BioMed Central

Research article

Open Access

Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria

Matthew E Falagas*[1,2,3], Ioannis A Bliziotis[3], Sofia K Kasiakou[3], George Samonis[4], Panayiota Athanassopoulou[3] and Argyris Michalopoulos[5]

- Olgu 1: Santral venöz katater

  Kolistin+ Meropenem

  Kür

- Olgu 2: Pnömoni

  Kolistin + Amp-Sulbaktam+ TMP-SXT

  Acinetobacter süperinfeksiyonu

  Sepsise bağlı mortalite

SYNERGISTIC ACTIVITY AND EFFECTIVENESS OF A DOUBLE-CARBAPENEM REGIMEN IN PANDRUG-RESISTANT *KLEBSIELLA PNEUMONIAE* BLOODSTREAM INFECTIONS

- 3 kan dolaşımı infeksiyonu , Meropenem MIC:128mg/L
- Olgu1 : Meropenem 3x2 gm, Ertapenem 1x1 gm

  21 gün tedavi- şifa
- Olgu2: Meropenem 2X1 gm,Ertapenem 1x500 mg (kreatinni klrensine göre doz ayarı)48 saatde ateş ve üreme yok-2 gün sonra exitus-akut kalp yetmezliği
- Olgu 3: Meropenem 3x2 gm, Ertapenem 1x1 gm

  24 gün tedavi-tam şifa

Olivia et all. JAC,2014;69(6):1718-20

Case Report

Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen

Alessandra Oliva [a], Maria T. Mascellino [a], Alessia Cipolla [a], Alessandra D'Abramo [a], Annalisa De Rosa [a], Stefano Savinelli [a], Maria Rosa Ciardi [a], Claudio M. Mastroianni [a,b,*], Vincenzo Vullo [a]

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[b] *UOC Malattie Infettive, Fondazione Eleonora Lorillard Spencer Cenci, Sapienza Università, Latina, Italy*

- 75 yaşında kadın hasta
- Geç dönem protez enfeksiyonu-MRKNS
- IV Rifampisin ve Daptomisin
- Yatışının 15.günüde ateş, hipotansiyon ve taşikardi

Case Report

Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen

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[b] *UOC Malattie Infettive, Fondazione Eleonora Lorillard Spencer Cenci, Sapienza Università, Latina, Italy*

- Kan ve idrar kültüründe Kolistin dirençli K.pneumoniae
- Santral venoz katater kültüründe Kolistin dirençli K.pneumonia ve Kolistin duyarlı Acinetobacter
- Ertapenm MIC:128 µg/ml, Meropenem MIC 256 µg/ml,Kolistin MIC 32 µg/ml

Case Report

Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen

Alessandra Oliva [a], Maria T. Mascellino [a], Alessia Cipolla [a], Alessandra D'Abramo [a], Annalisa De Rosa [a], Stefano Savinelli [a], Maria Rosa Ciardi [a], Claudio M. Mastroianni [a,b,*], Vincenzo Vullo [a]

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[b] *UOC Malattie Infettive, Fondazione Eleonora Lorillard Spencer Cenci, Sapienza Università, Latina, Italy*

- Ertapenem 1gm, Meropenem 3x2 gm
- Kolistin 6.000.000 IU yükleme, 2x4.500.000 IU
- Tedavinin 96. saatinde afebril, sedim –crp düşmekte
- 7.günde Kolistin kesiliyor- Görsel halüsinasyon
- İkili karbapenem 14 gün daha devam ediliyor
- Tedaviye cevap-yeni eklem protezi için transfer

Case Report

Therapeutic strategy for pandrug-resistant *Klebsiella pneumoniae* severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen

Alessandra Oliva [a], Maria T. Mascellino [a], Alessia Cipolla [a], Alessandra D'Abramo [a], Annalisa De Rosa [a], Stefano Savinelli [a], Maria Rosa Ciardi [a], Claudio M. Mastroianni [a,b,*], Vincenzo Vullo [a]

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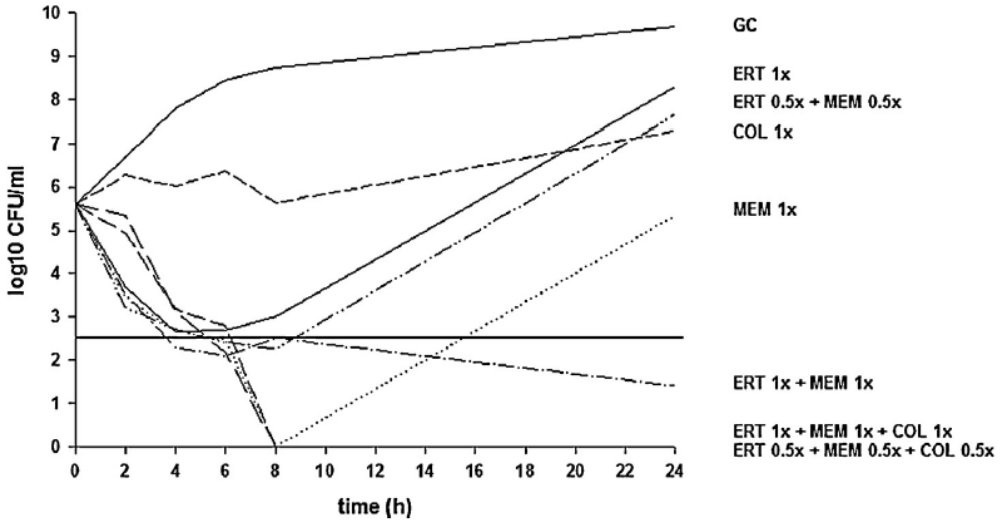

Figure 1. Time–kill studies for ertapenem, meropenem, colistin, ertapenem plus meropenem, and ertapenem plus meropenem plus colistin against pandrug-resistant *Klebsiella pneumoniae* isolated from a patient with a bloodstream infection. The horizontal line represents a reduction of 3 $\log_{10}$ CFU/ml compared with the initial bacterial count. GC, growth control; MEM, meropenem; ETP, ertapenem; COL: colistin.

Research Article

Emergence of Carbapenem-Resistant *Klebsiella pneumoniae*: Progressive Spread and Four-Year Period of Observation in a Cardiac Surgery Division

BioMed Research International

Fortunata Lombardi,[1] Paola Gaia,[2] Rea Valaperta,[1] Maria Cornetta,[2] Milvana Rosa Tejada,[2] Luca Di Girolamo,[1] Alessandra Moroni,[2] Federica Ramundo,[2] Alessio Colombo,[3] Massimiliano Valisi,[3] and Elena Costa[1,2]

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[3] Service Lab Fleming Research, Milan, Italy

- Şubat 2010-Aralık 2013
- 280 K.pneumonia
- %1 Kol-R K.pneumonia
- Kolistin kullanım öyküsü
- Double Karbapenem tedavisi

Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Giancarlo Ceccarelli,[a] Marco Falcone,[b] Alessandra Giordano,[a] Maria Lina Mezzatesta,[c] Carla Caio,[c] Stefania Stefani,[c] Mario Venditti[a]

Department of Public Health and Infectious Diseases, Policlinico Umberto I, University of Rome Sapienza, Rome, Italy[a]; Department of Emergency Medicine, Policlinico Umberto I, University of Rome Sapienza, Rome, Italy[b]; Department of Bio-Medical Sciences, University of Catania, Catania, Italy[c]

- 65 yaşında erkek-Serebral hemoraji-Subepandimom operasyonu
- Kan ve ETA :Kol-R K.pneumonia
- Kolistin (9MIU yükleme-2X4.5MIU),Meropenem 3x2 gm,Rifampisin 3x300 mg--6gün
- Kolistin +Fosfomisin 3x3g -----5 gün

Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Giancarlo Ceccarelli,[a] Marco Falcone,[b] Alessandra Giordano,[a] Maria Lina Mezzatesta,[c] Carla Caio,[c] Stefania Stefani,[c] Mario Venditti[a]

Department of Public Health and Infectious Diseases, Policlinico Umberto I, University of Rome Sapienza, Rome, Italy[a]; Department of Emergency Medicine, Policlinico Umberto I, University of Rome Sapienza, Rome, Italy[b]; Department of Bio-Medical Sciences, University of Catania, Catania, Italy[c]

- Ateş, bakteriyemi,MODS
- Kan kültürlerinde aynı etken
- **Ertepenem** 1x500 mg, **Doripenem** 3x250 mg (4 saatlik infüzyon) 4 hafta
- Ateş 4.günde, bakteri eradikasyonu 8.günde
- Ertapenem+ Doripenem sinerjik etki

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Antimicrobial Agents and Chemotherapy p. 2388–2390

Helen Giamarellou, Lambrini Galani, Fotini Baziaka, Ilias Karais[illegible]

6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

May 2013 Volume 57 Number 5

- Olgu 1: Kan ,santral venöz katater ve idrar kültürü
- **Ertapenem** 1x1 gm,**Doripenem** 3x2gm- (Ertapenemden 1 saat sonra)- 4 saatlik infüzyon- 20 gün tedavi
- 4.günde ateş yanıtı, 2.günde bakteri eradikasyonu
- 10 ay içinde relaps yok

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Helen Giamarellou, Lambrini Galani, Fotini Baziaka, Ilias Karaiskos

6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

Olgu 2: Kan ve idrar **kültürü Ertapenem** 1x1 gm, **Meropenem** 3x1 gm (Ertapenemden 1 saat sonra)- 3 saatlik infüzyon

- 14- gün tedavi
- 3.gün ateş yanıtı, tedavi süresince ve 3 hafta sonraya kadar kültürler steril,

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Helen Giamarellou, Lambrini Galani, Fotini Baziaka, Ilias Karaiskos

6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

- Olgu 3: Spinal kord yaralanması-aralıklı kataterizasyon uygulaması
- İdrar kültürü
- Ertapenem 1x1 gm, Meropenem 3x2gm (Ertapenemden 1 saat sonra)-3 saatlik infüzyon-10 gün tedavi
- Tedavinin 2.gününde idrar steril, 6 ay içinde relaps yok

Outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals

M. L. Mezzatesta[1], F. Gona[1], C. Caio[1], V. Petrolito[1], D. Sciortino[1], A. Sciacca[2], C. Santangelo[3] and S. Stefani[1]
1) Department of Bio-Medical Sciences, Section of Microbiology, University of Catania, 2) University Hospital and 3) Vittorio Emanuele Hospital, Catania, Italy

- 2 sicilya hastanesi
- Kolistin-R Klebsiella infeksiyonu 8,

  rektal veya farenks kolonizasyonu 3
- Yoğun Bakım,Cerrahi,Transplantasyon,Çocuk hematoloji ve iç hastalıkları klinikleri
- Bla-kpc3
- PFGE-1 Klon-ST258

TABLE I. Clinical characteristics of patients and antibiotic susceptibility of KPC-3-producing *Klebsiella pneumoniae*

Patients	Date	Hospital	Ward	Specimens	MIC (mg/L)											
					IPM	MEM	DOR	ETP	CEF	CAZ	CTX	TZP	TG	CT	CIP	GM
1	19 August 2010	University	ICU	Abdominal drainage	32	64	64	>128	128	>64	>64	>512	1	16	128	2
2	31 August 2010	University	Surgery	CVC	64	64	64	>128	>128	>64	>64	>512	1	32	128	2
3	10 September 2010	University	ICU	Bloodstream	64	128	64	128	>128	>64	>64	>512	1	16	128	2
4	19 September 2010	University	ICU	Bronchial aspirate	64	64	32	>128	>128	>64	>64	>512	1	32	128	2
5	20 September 2010	University	Internal Medicine	Urine	64	64	64	>128	>128	>64	>64	>512	1	8	256	2
6	23 September 2010	University	Transplant	Sputum	32	64	128	128	128	>64	>64	>512	1	64	128	2
7	26 September 2010	University	Paediatric Haematology	Bloodstream	64	64	256	>128	128	>64	>64	>512	1	32	128	2
8	19 October 2010	VE	Nephrology	Bloodstream	128	512	64	512	512	>512	256	>512	1	8	256	2
3[a]	20 October 2010	University	ICU	Pharyngeal swab	32	64	64	128	128	>64	>64	>512	1	32	128	2
7[a]	26 October 2010	University	Paediatric Haematology	Rectal swab	>512	>512	64	>512	256	>512	256	>512	1	8	128	2
4[a]	27 October 2010	University	ICU	Rectal swab	64	512	64	512	512	>512	256	>512	1	16	128	2

IPM, imipenem; MEM, meropenem; DOR, doripenem; ETP, ertapenem; CEF, cefepime; CAZ, ceftazidime; CTX, cefotaxime; TZP, piperacillin–tazobactam; TG, tigecycline; CT, colistin; CIP, ciprofloxacin; GM, gentamicin; VE, Vittorio Emanuele; CVC, central venous catheter; ICU, intensive-care unit.
[a]Colonization.

Gentamisin+tigesiklin +/-karbapenem+/-Gram pozitif etkili antibiyotik kombinasyonu

İnfeksyona bağlı mortalite yok(1 hasta da enfeksiyon dışı nedenden mortalite)

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Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

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- Retrospektif gözlemsel, kohort çalışması
- 750 yataklı hastane
- 1 temmuz 2012-15 şubat 2013
- 50 sepsis hastası
- 30günlük mortalite %38

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

- Tigesiklin duyarlılığı %72(n30)
- Fosfomisin duyarlılığı%20(n:10)
- Gentamisin MIC <2: %36(n:18)

  MIC 2-4:%62(n:31)

  MIC>4 : %2(n:1)

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Table 1. Baseline characteristics of 50 patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae*: univariate analysis of factors associated with crude mortality at 30 days

	Number (%) of patients (unless otherwise stated)				
	total ($n=50$)	no survivors ($n=19$)	survivors ($n=31$)	P	HR (95% CI)
Demographic variables					
age (years), median (range)	**60.5 (19–86)**	**67 (41–86)**	**55 (19–85)**	**0.046**	**1.03 (1.00–1.06)**
male	32 (64.0)	12 (63.2)	20 (64.5)	0.971	0.98 (0.38–2.49)
Comorbidities					
Charlson index, median (range)	4 (0–11)	4 (0–11)	3 (0–8)	0.178	1.13 (0.95–1.35)
renal failure[a]	**16 (32.0)**	**10 (52.6)**	**6 (19.4)**	**0.008**	**3.44 (1.39–8.54)**
Previous hospitalization (3 previous months)	**16 (32.0)**	**10 (52.6)**	**6 (19.4)**	**0.022**	**2.88 (1.16–7.14)**
Admission to the ICU	22 (44.0)	8 (42.1)	14 (45.2)	0.671	1.16 (0.59–2.59)
Invasive procedures (in previous week)					
mechanical ventilation	26 (52.0)	10 (52.6)	16 (51.6)	0.644	1.24 (0.49–3.16)
central venous catheter	36 (72.0)	11 (57.9)	25 (80.6)	0.349	0.62 (0.23–1.68)
urinary catheter	46 (92.0)	17 (89.5)	29 (93.5)	0.893	0.90 (0.21–3.92)
Prior antibiotic therapy (in the previous month)					
quinolones	**21 (42.0)**	**12 (63.2)**	**9 (29.0)**	**0.043**	**2.63 (1.03–6.71)**
amoxicillin/clavulanic acid	14 (28.0)	3 (15.8)	11 (35.5)	0.132	0.42 (0.12–1.43)
meropenem	23 (46.0)	9 (47.4)	14 (45.2)	0.764	1.14 (0.46–2.82)
cephalosporins	12 (24.0)	7 (36.8)	5 (16.1)	0.071	2.36 (0.93–6.02)
piperacillin/tazobactam	13 (26.0)	6 (31.6)	7 (22.6)	0.461	1.44 (0.55–3.79)

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Type of infection					
pneumonia	24 (48.0)	8 (42.1)	16 (51.6)	0.356	1.07 (0.93–1.23)
purulent tracheobronchitis	4 (8.0)	1 (5.3)	3 (9.7)		
urinary tract infection	10 (20.0)	5 (26.3)	5 (16.1)		
surgical wound infection	4 (8.0)	1 (5.3)	3 (9.7)		
intra-abdominal infection	1 (2.0)	1 (5.3)	0 (0)		
infection of skin and soft tissue	1 (2.0)	0 (0)	1 (3.2)		
endocarditis	1 (2.0)	1 (5.3)	0		
primary or catheter-related bacteraemia	4 (8.0)	2 (10.5)	2 (6.5)		
infection of the CNS	1 (2.0)	0	1 (3.2)		
Bacteraemia	18 (36.0)	7 (36.8)	11 (35.5)	0.866	1.08 (0.43–2.57)
Severe sepsis/septic shock	**30 (60.0)**	**18 (94.7)**	**12 (38.7)**	**0.006**	**16.6 (2.21–125.1)**
CL_{CR} at start of antibiotic treatment (mL/min), mean ± SD	**96.2 ± 53.2**	**69.4 ± 38.0**	**112.6 ± 55.0**	**0.005**	**0.98 (0.97–0.99)**
Active empirical treatment	6 (12.0)	2 (10.5)	4 (12.9)	0.857	0.87 (0.20–3.78)
Time to initiation of optimal targeted treatment (days), mean (range)	2.1 (0–5)	1.7 (0–5)	2.2 (0–5)	0.405	0.86 (0.61–1.22)
Optimal targeted treatment	**37 (74.0)**	**9 (47.4)**	**28 (90.3)**	**0.001**	**0.18 (0.07–0.45)**
monotherapy	16 (32.0)	4 (21.1)	12 (38.7)	0.258	0.53(0.18–1.60)
tigecycline	8 (16.0)	3 (15.8)	5 (16.1)		
gentamicin	8 (16.0)	1 (5.3)	7 (22.6)		
combination therapy	21 (42.0)	5 (26.3)	16 (51.6)	0.058	0.37 (0.13–1.03)
tigecycline + gentamicin	21 (42.0)	5 (26.3)	16 (51.6)		
Optimal targeted treatment with tigecycline	29 (58.0)	8 (42.1)	21 (67.7)	0.059	0.41 (0.16–1.03)
Optimal targeted treatment with high-dose tigecycline	10 (20.0)	1 (5.3)	9 (29.0)	0.098	0.18 (0.20–1.37)

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Meropenem MIC>32 mg/L

3X1 gm dozda

	Number (%) of patients (unless otherwise stated)				
	total (n=50)	no survivors (n=19)	survivors (n=31)	P	HR (95% CI)
Targeted treatment with meropenem	11 (22.0)	9 (47.4)	2 (6.4)	<0.001	6.02 (2.37–15.28)
Optimal targeted treatment with gentamicin	**29 (58.0)**	**6 (31.6)**	**23 (74.2)**	**0.002**	**0.21 (0.08–0.57)**
MIC ≤2 mg/L	**13 (26.0)**	**1 (5.3)**	**12 (38.7)**	**0.009**	**0.05 (0.01–0.47)**
MIC >2 to ≤4 mg/L	16 (32.0)	5 (26.3)	11 (35.5)	0.133	0.42 (0.14–1.30)

Variables with a statistically significant different distribution between survivors and non-survivors are shown in bold.
[a]CL_{CR} calculated using the Cockroft–Gault formula.

Table 2. Antibiotics used in 50 patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae*

	Number (%) of patients					
	optimal	mortality	suboptimal	mortality	total	mortality
Empirical treatment	6 (8.0)	2 (33.3)	44 (92.0)	17 (38.6)	50	19 (38.0)
tigecycline	4 (66.6)	2 (50.0)	0	0	4 (8.0)	2 (50.0)
tigecycline + gentamicin	2 (33.3)	0	0	0	2 (4.0)	0
fosfomycin	0	0	1 (2.2)	0	1 (2.0)	0
meropenem	0	0	18 (40.9)	8 (44.4)	18 (36.0)	8 (44.4)
piperacillin/tazobactam	0	0	7 (15.9)	0	7 (14.0)	0
amoxicillin/clavulanic acid	0	0	2 (4.5)	0	2 (4.0)	0
others	0	0	16 (36.4)	9 (56.2)	16 (32.0)	9 (56.2)
Targeted treatment	37 (74.0)	9 (24.3)	13 (26.0)	10 (76.9)	50	19 (38.0)
monotherapy	16 (43.2)	4 (25.0)	6 (46.2)	5 (83.3)	22 (44.0)	9 (40.9)
tigecycline	8 (21.6)	3 (37.5)	1 (7.7)	0	9 (18.0)	3 (33.0)
high-dose tigecycline	3 (8.1)	0	0	0	3 (6.0)	0
gentamicin	8 (21.6)	1 (12.5)	0	0	8 (16.0)	1 (12.5)
meropenem	0	0	5 (38.5)	5 (100)	5 (10.0)	5 (100)
combination therapy	21 (56.7)	5 (23.8)	7 (53.8)	5 (71.4)	28 (56.0)	10 (35.7)
tigecycline + gentamicin	21 (56.7)	5 (23.8)	0	0	21 (42.0)	5 (23.8)
high-dose tigecycline	7 (18.9)	1 (14.3)	0	0	7 (14.0)	1 (14.3)
meropenem + fosfomycin	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
tigecycline + colistin	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
high-dose tigecycline	0	0	1 (7.7)	1 (100)	1 (2.0)	1 (100)
meropenem + colistin ± fosfomycin	0	0	5 (38.5)	3 (60.0)	5 (10.0)	3 (60.0)

Duyarlı olduğunda Gentamisin erken kullanımı kaba mortaliteyi etkileri

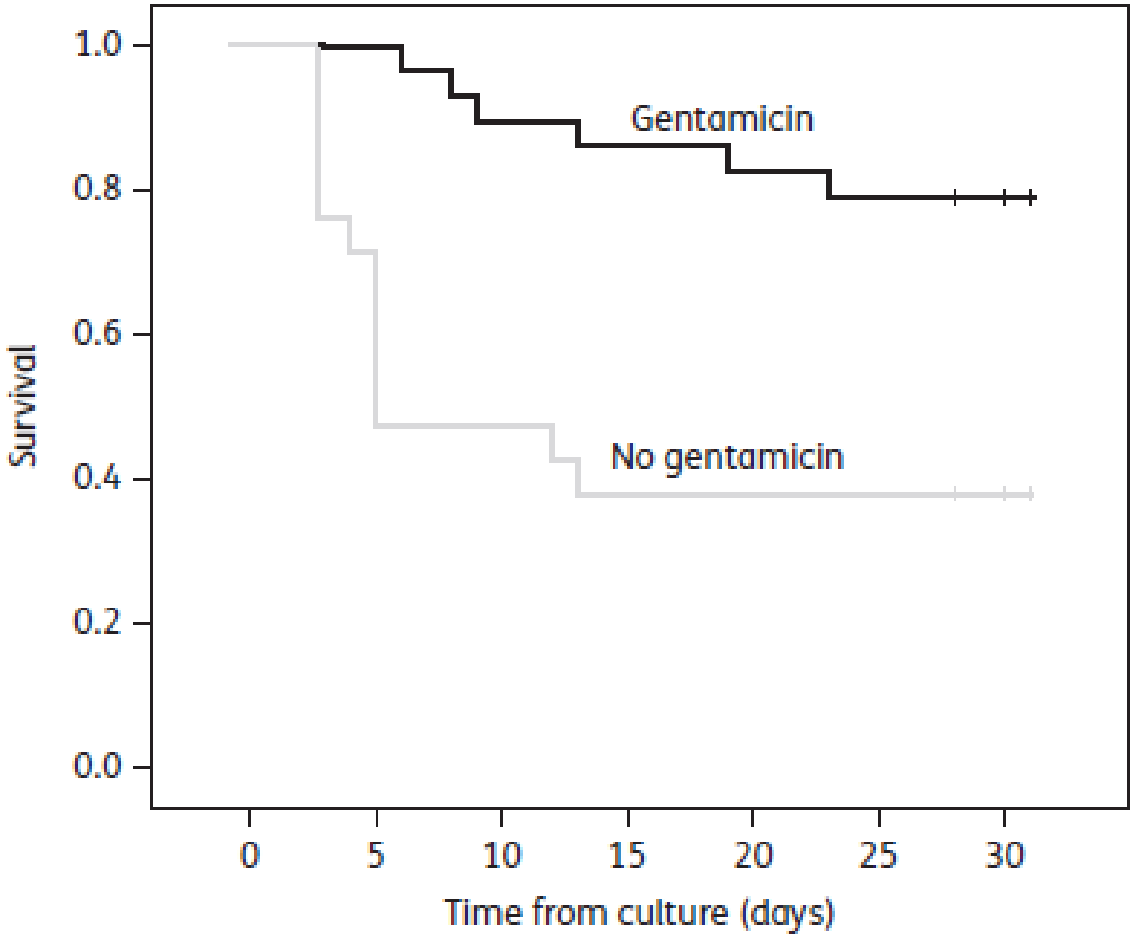

Figure 1. Kaplan–Meier curves showing the impact of targeted treatment with gentamicin on survival at 30 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae* (log-rank test 11.9, $P = 0.001$).

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Distribution of β-Lactamase Genes Among Carbapenem-Resistant *Klebsiella pneumoniae* Strains Isolated From Patients in Turkey

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- 37 CRE izolat (%2.7 kolistin direnci)
- Ekim 2012, 1 hasta kan kültüründe üreme, Tigesiklin ve SXT duyarlı, bla_{OXA-48} bla_{CTX-M2} bla_{TEM} bla_{SHV}
- Tigesiklin ve Sefaperazon-Sulbactam tedavisi, exitus

FOSFOMİSİN

- Eski bir antibiyotik
- İdrar ve serumda yüksek seviye
- Hızla dokulara yayılır
  - böbrek, mesane, prostat, akciğer, iltihaplı doku, kemik, beyin omurilik sıvısı, abse sıvısı ve kalp dokusu
- Monoterapi ile hızla direnç gelişebilir

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0066-4804/10/$12.00 doi:10.1128/AAC.01235-09

In Vitro Activity of Fosfomycin against *bla*$_{KPC}$-Containing *Klebsiella pneumoniae* Isolates, Including Those Nonsusceptible to Tigecycline and/or Colistin$^{\nabla}$

Andrea Endimiani,[1,2]* Gopi Patel,[3] Kristine M. Hujer,[1,2] Mahesh Swaminathan,[3] Federico Perez,[1,2] Louis B. Rice,[2] Michael R. Jacobs,[4] and Robert A. Bonomo[1,2,5,6]*

- 68 KPC izolatı, in vitro çalışma
- 23 izolat kolistin ve veya tigesiklin dirençli
- 6 suş XDR(5 kolistin ve tigesiklin fuyarlı)
- Fosfomisin genel duyarlılık %92.6
- Kombinasyon tedavi

Table 6. Drug in Late Stage (Phase 3) Clinical Development With Activity Against Carbapenem-Resistant *Enterobacteriaceae*

Drug	Class	Stage of Development	Carbapenemase Spectrum	Phase III Studies	Proposed Dose
Ceftazidime-avibactam	Cephalosporin-β-lactamase inhibitor	Phase 3	Activity against KPCs and OXA-48 (not active against MBLs)	• Ceftazidime-avibactam + metronidazole vs meropenem for cIAI • Ceftazidime-avibactam + metronidazole vs meropenem for NP • Ceftazidime-avibactam vs doripenem for cUTI	IV: 2000 mg (ceftazidime)/500 mg (avibactam) q8h
Ceftaroline-avibactam	Cephalosporin-β-lactamase inhibitor	Entering Phase 3	Active against KPCs and OXA-48 (not active against MBLs)	• Ceftaroline- avibactam vs doripenem for cUTI (Phase II study, proposed Phase III studies not yet available)	IV: 600 mg (ceftaroline)/600 mg (avibactam) q8h
Plazomicin	Aminoglycoside	Phase 3	Active against most KPCs (not active against many NDMs)	• Plazomicin vs colistin when combined with a second antibiotic (either meropenem or tigecycline) for CRE BSI or NP	IV: 10–15 mg/kg q24h
Eravacycline	Tetracycline	Phase 3	Active against KPCs	• Eravacycline vs ertapenem for cIAI • Eravacycline vs levofloxacin for cUTI	IV: 1.0 mg/kg q12h or 1.5 mg/kg q24h PO: 200–250 mg q12h

Abbreviations: BSI, bloodstream infection; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant enterobacteriaceae; cUTI, complicated urinary tract infection; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NP, nosocomial pneumonia; OXA, oxacillinase; IV, intravenous; PO, oral.

In vitro activity of the next-generation aminoglycoside plazomicin alone and in combination with colistin, meropenem, fosfomycin or tigecycline against carbapenemase-producing Enterobacteriaceae strains☆

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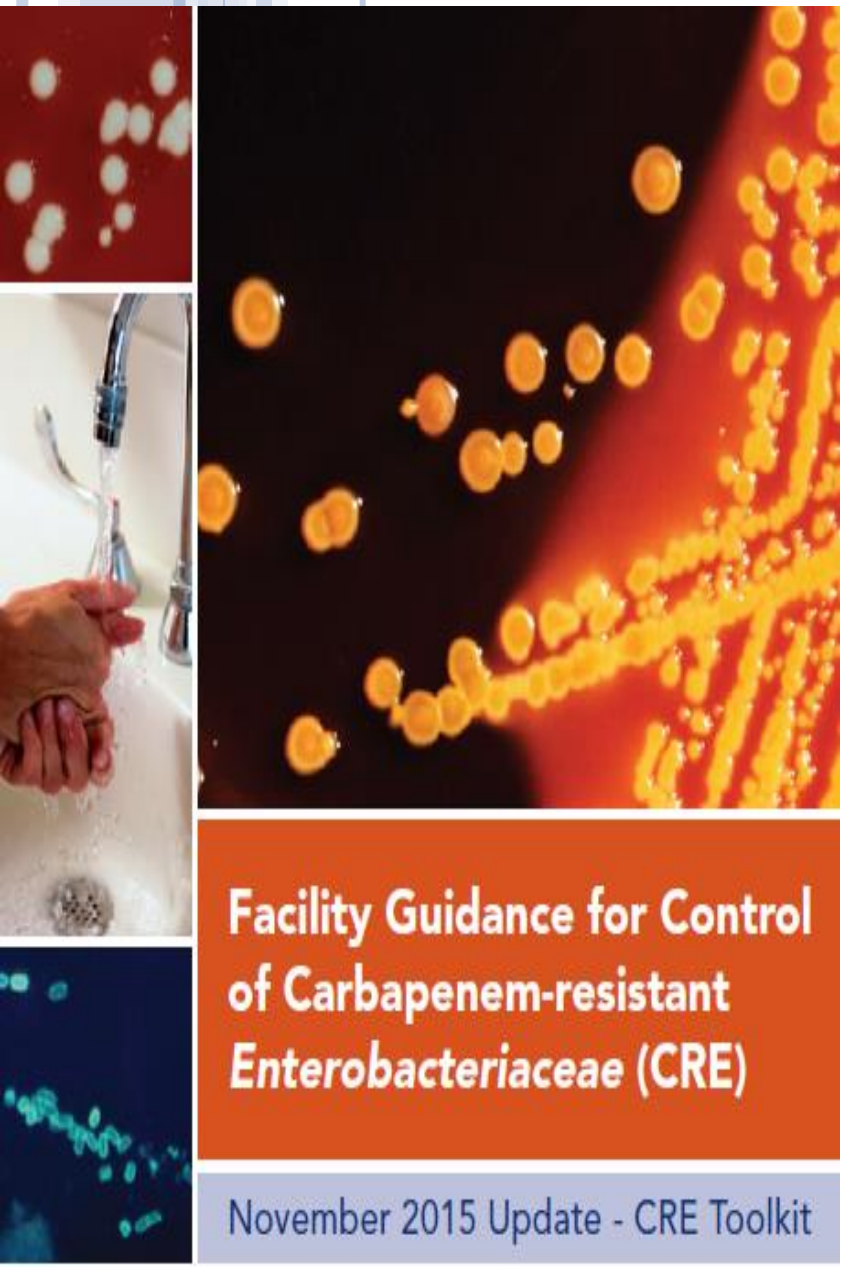
- Yeni jenerasyon aminoglokozid
- Faz 3 çalışmalar
- Kolistin,Meropenem ve Fosfomisin ile sinerjik etki, bakterisidal etkide artış



1- Sürveyans

2-İnfeksiyon Kontrol Önlemleri