Antimikrobiyallere Dirençli Bakterilerde Fenotip/Genotipe Göre Tedavi Algoritmaları ve Kısıtlı Kaynak Bilmecesi : Nasıl Yapmalı ?

Kolistin Dirençli Gram-Negatif Çomaklar

Dr Gökhan AYGÜN

İUC-Cerrahpaşa Tıp Fakültesi

Tıbbi Mikrobiyoloji AD

ORIGINAL ARTICLE BACTERIOLOGY

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carmeli[3], M. E. Falagas[4,5], C. G. Giske[6], S. Harbarth[7], J. F. Hindler[8], G. Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. B. Rice[12], J. Stelling[13], M. J. Struelens[1], A. Vatopoulos[14], J. T. Weber[2] and D. L. Monnet[1]

- Kolistin, Fosfomisin dahil ….PDR

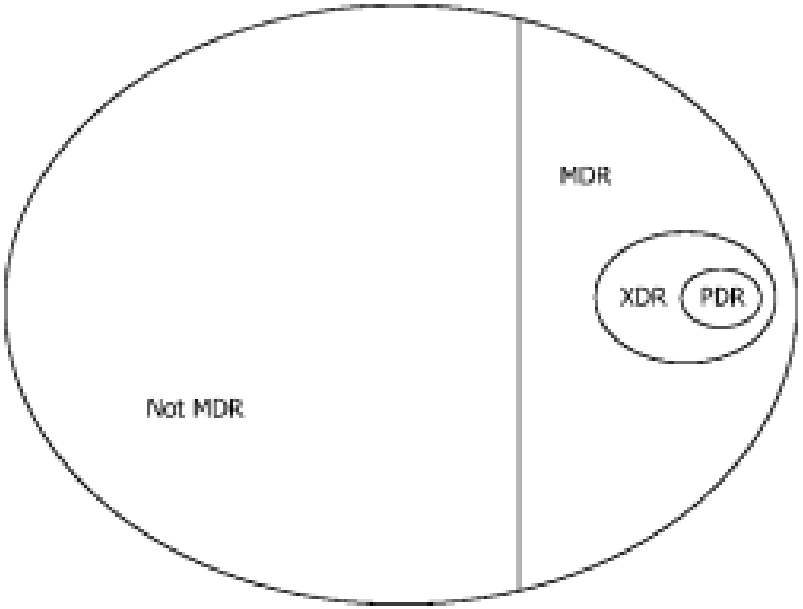


FIG. 1. Diagram showing the relationship of MDR, XDR and PDR to each other.

Clinical Microbiology and Infection,
Volume 18 Number 3, March 2012

Bilinenler

- Artan ölüm (EU 25.000 ölüm/2018 yılı)
- Artan masraf (1.5 milyar Euro ekstra harcama)

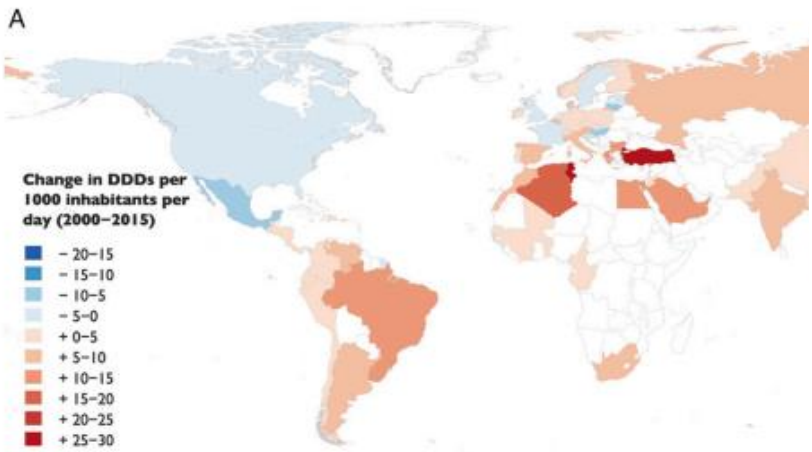
- Artmaya devam eden direnç
- Yayılan yeni, dirençli, virulan klonlar

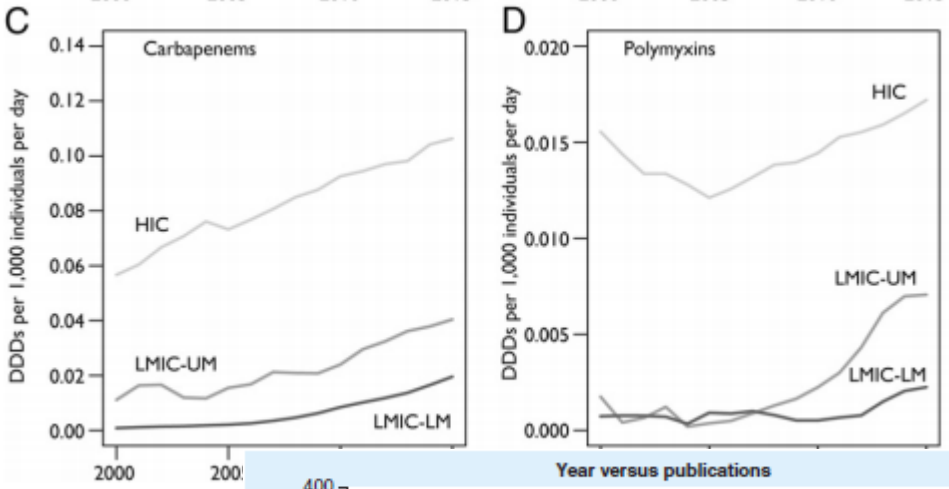
- «POST-ANTİBİYOTİK ÇAĞ»

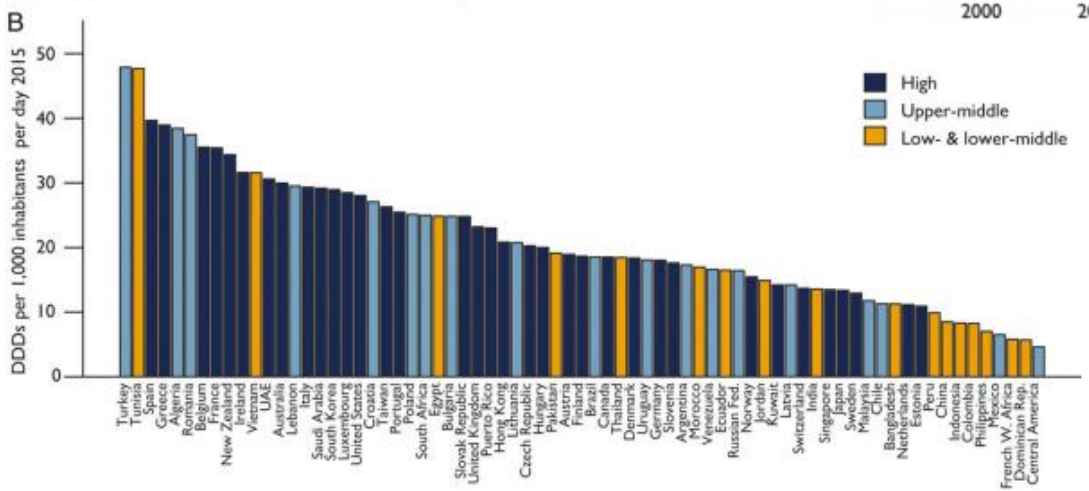
Bilinenler-Çok antibiyotik çok direnç !!!

Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein[a,b,c,1], Thomas P. Van Boeckel[d], Elena M. Martinez[a], Suraj Pant[a], Sumanth Gandra[a], Simon A. Levin[e,f,g,1]







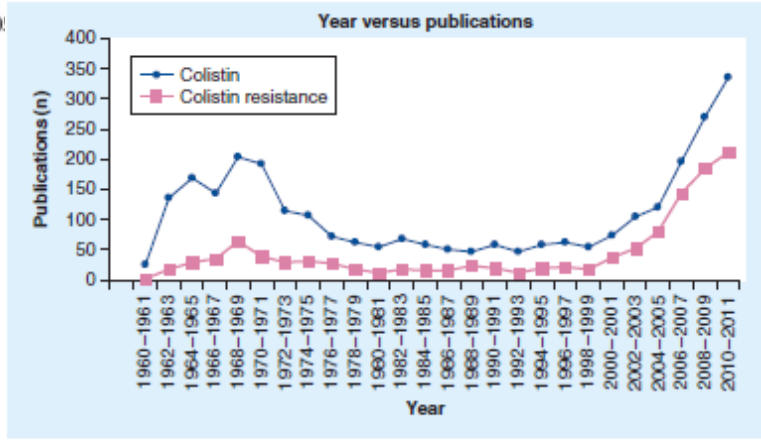


Figure 1. Number of citations found in the Pubmed database from 1960 to the middle of 2011 using either the term 'colistin' or 'colistin resistance'.

Uzun süreçli planlar

- «Tek Tıp» ile global direnç mücadelesi
- Antimikrobiyal Yönetim Programları
- Tıp alanında teknolojik gelişmeler
- Tıp Eğitimi
- İnsanlığı tehdit eden sorun algısı
- …

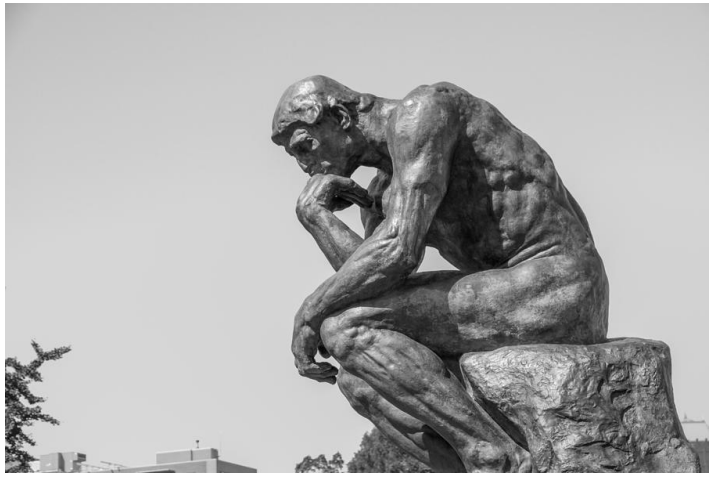
Beklenenler

- Yeni antibiyotikler !

- Yeni tedavi yaklaşımları (FAJ)
- Virulansa müdahele (microbiota, QS inhibisyonu,…)

Elimizdekiler

- Elimizdeki antibiyotikleri akılcı kullanmak
  KOLİSTİN
  (Fosfomisin,Tigesiklin,…)



- İnfeksiyon Kontrolü
  !!!

Kolistin-Polimiksin

- Siklik polipeptid
- Paenibacillus polymyxa……1947
- 1959 yılından itibaren kullanımda

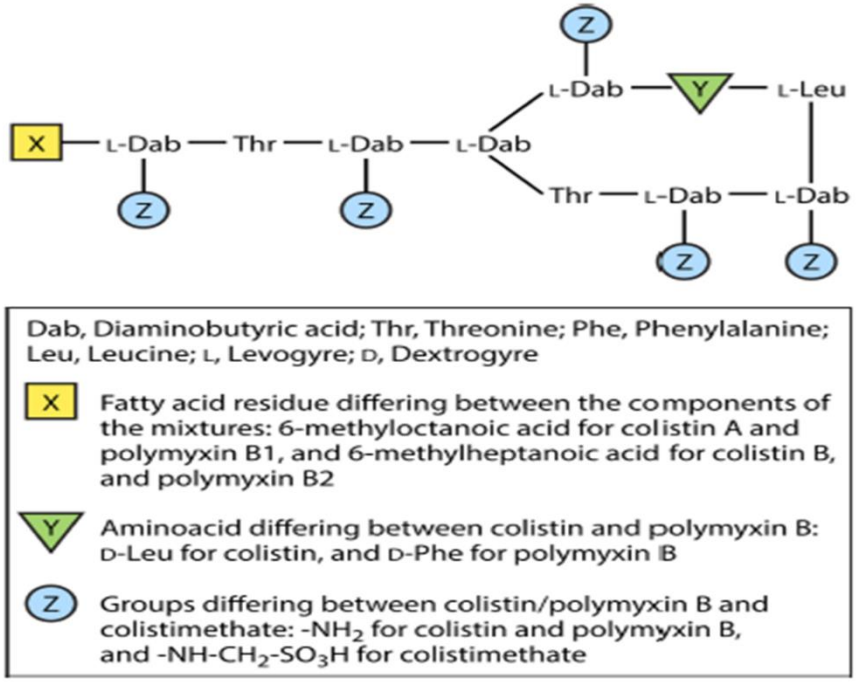


FIG 1 Structures of colistin A and B, colistimethate A and B, and polymyxin B1 and B2.

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

Polymyxins: Antibacterial Activity, Susceptibility Testing, and Resistance Mechanisms Encoded by Plasmids or Chromosomes

Laurent Poirel,[a,b,c] Aurélie Jayol,[a,b,c] Patrice Nordmann[a,b,c,d]

Kolistin-Polimiksin

- Kolistin sülfat (oral)
- Kolistimetat sodyum (CMS) parenteral
- Polimiksin

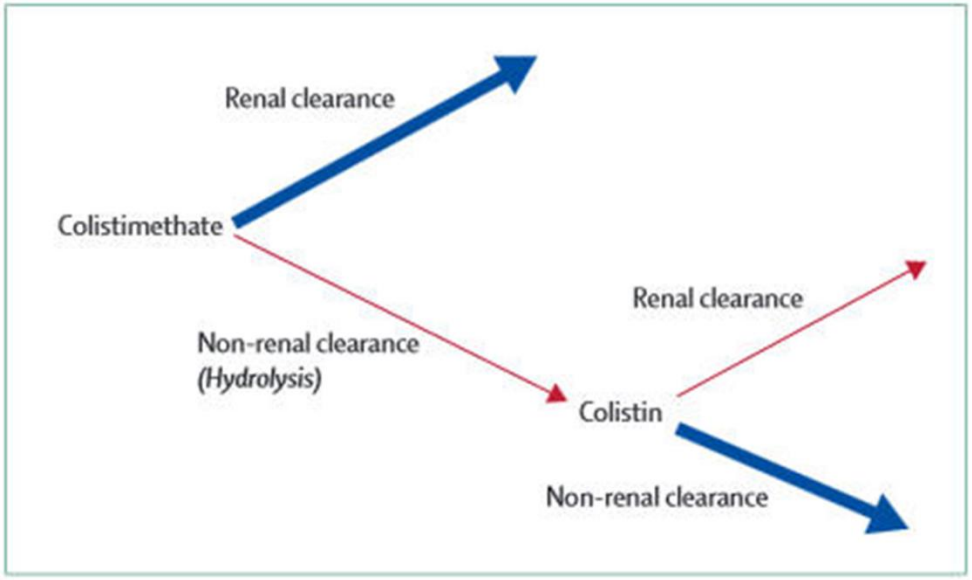
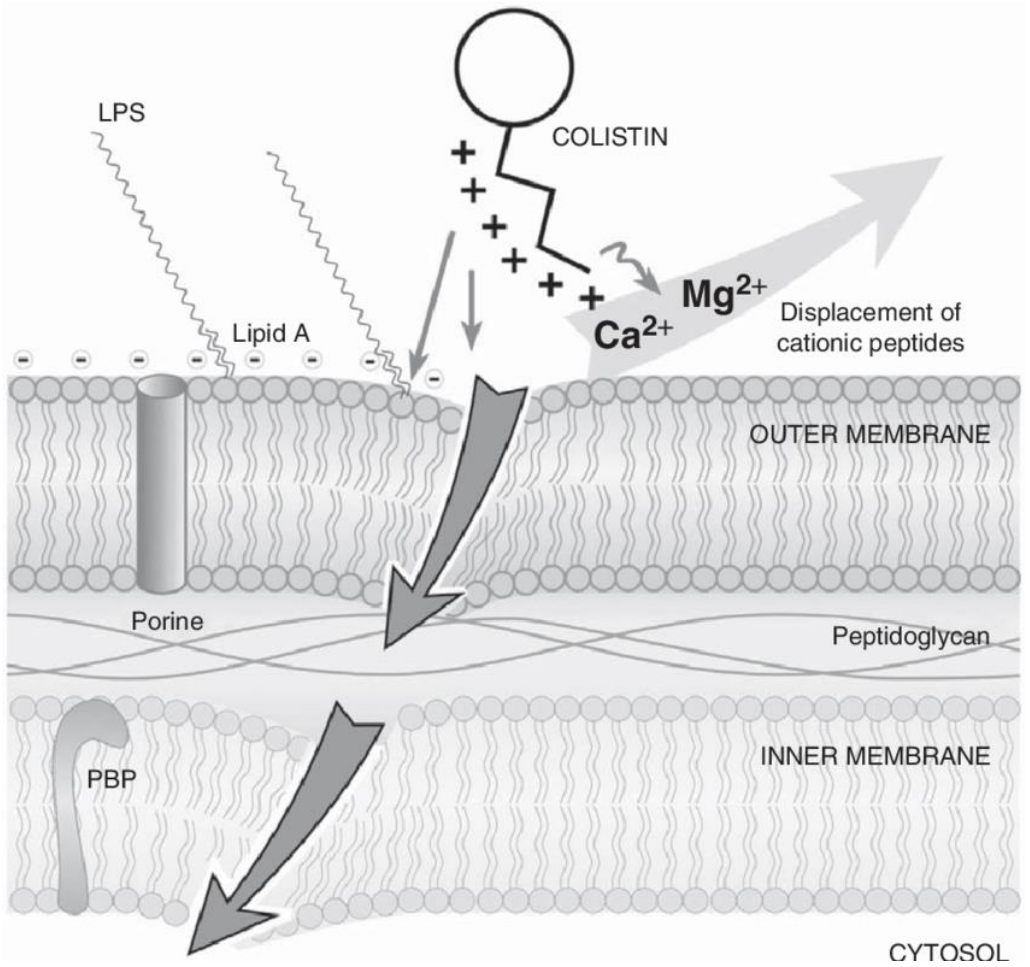


Figure 2: Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium

Etki Mekanizması

- Katyonik peptid olan kolistin, bakteri dış membranındaki anyonik LPS ile elektrostatik olarak etkileşir
- LPS'nin fosfat grupları içindeki Ca ve Mg iyonlarını dışarı çıkarır
- Permeabilite bozukluğu sonucu ölüm



Etki mekanizması

- Hızlı
- Bakterinin metabolik aktivitesinden bağımsız
- ANTİENDOTOKSİK etki
- A.baumannii izolatlarında hidroksil radikal üretimi ile hızlı ölüm !

CMRO
Current Medical Research & Opinion Vol. 31, No. 4, 2015, 707–721
0300-7995
Article ST-0415.R1/1018989
doi:10.1185/03007995.2015.1018989
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Review
Colistin, mechanisms and prevalence of resistance

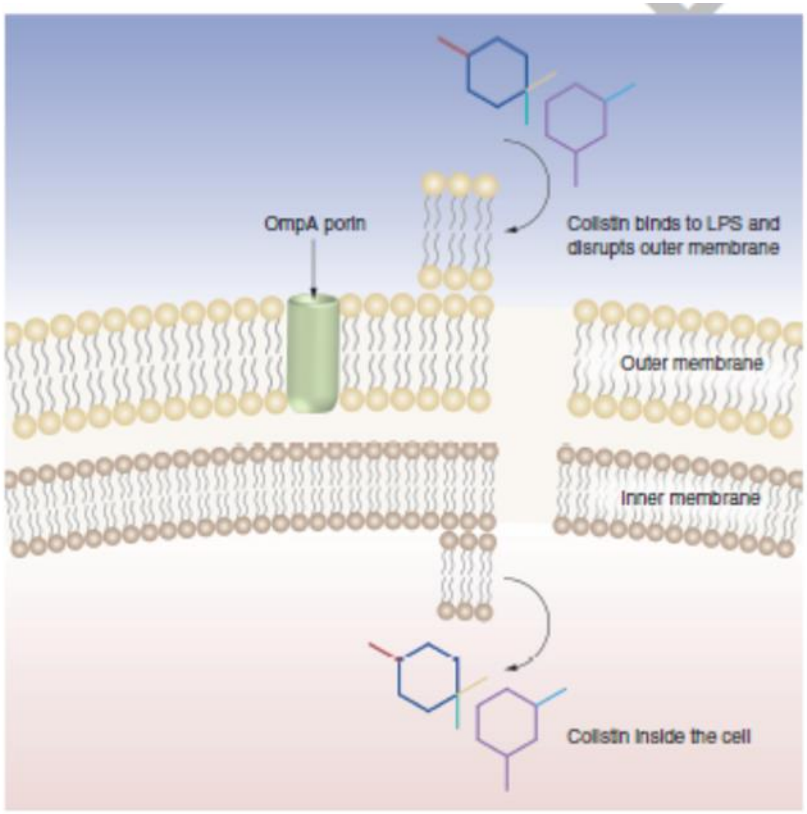

Figure 3. Antimicrobial mode of action of polymyxin against Gram-negative bacterial membranes.
LPS: Lipopolysaccharide.

Current Infectious Disease Reports (2018) 20: 10
https://doi.org/10.1007/s11908-018-0614-0

HEALTHCARE ASSOCIATED INFECTIONS (G BEARMAN AND D MORGAN, SECTION EDITORS)

Pharmacokinetic and Pharmacodynamic Considerations of Antibiotics of Last Resort in Treating Gram-Negative Infections in Adult Critically Ill Patients

Mojdeh S. Heavner[1] · Kimberly C. Claeys[1] · Anne M. Masich[1] · Jeffrey P. Gonzales[1]

Antibiotic	Target	Mechanism	Comments
Aminoglycosides [17–20]	C_{max}/ MIC	Concentration-dependent	Optimal ratio >/= 8–10/1
Polymyxins [38]	AUC/MIC	Concentration- and time-dependent	
Tigecycline [60–63]	AUC/MIC	Concentration- and time-dependent	
Fosfomycin [75]	%T > MIC	Time-dependent	Optimal ratio ≥ 2:1
Fluoroquinolones [98, 99]	AUC/MIC	Concentration- and time-dependent	Optimal ratio ≥ 125:1

CMS-DOZ ?

Colistimethate Sodium Conversion (EMA 2014)

Colistimethate Sodium	Colistimethate Sodium	Colistin-Base Activity (CBA)
12,500 units	1 mg	0.4 mg
150,000 units	12 mg	5 mg
1,000,000 units	80 mg	34 mg
4,500,000 units	360 mg	150 mg
9,000,000 units	720 mg	300 mg

COLİMYCİN 150 mg İ.M./İ.V. Enjeksiyon ve İnhalasyon İçin Liyofilize Toz İçeren Flakon

Steril-Apirojen

Kas içine ya da damar içine enjekte edilir.

- ***Etkin madde:*** Her bir flakon 150 mg kolistin bazına eşdeğer miktarda kolistimetat sodyum içerir.
- ***Yardımcı maddeler:*** Enjeksiyonluk su

Susceptible infections: IM, IV: 2.5 to 5 mg CBA/kg/day in 2 to 4 divided doses; maximum: 5 mg CBA/kg/day

Severe infections (due to multidrug-resistant organisms susceptible to colistin in the critically ill) (off-label dosing): IV: Loading dose: 300 mg CBA followed by 150 mg CBA twice daily (Dalfino 2012; Plachouras 2009). Additional trials may be necessary to further evaluate the use of this dosing in critically ill patients with this condition.

CMS (Colistine base) doz

- UK önerisi…. 60 kg > … 80-160 mg x 3
- 2-3 mg/kg her HD sonrası
- 2 mg/kg/gün PD hastasında

Stanford Health Care Antimicrobial Dosing Reference Guide

This document is also located on the SHC Intranet (http://portal.stanfordmed.org/depts/AntimicrobialStewardshipProgram) and http://bugsanddrugs.stanford.edu • ABX Subcommittee Approved: March 2017

Drug	CrCl > 50 mL/min	CrCl 10 – 50 mL/min	CrCl < 10 mL/min	Intermittent Hemodialysis (IHD)	CRRT
Colistin (IV)[1–3,20–22] **(SHC Restriction)** (Dosage expressed in terms of colistin base activity [CBA]; **Use ideal BW in obese)**	**U.S. FDA Package Insert** CrCl > 80: Loading Dose: 5 mg/kg x 1 (max dose: 300 mg); Maintenance Dose: 1.25 – 2.5 mg/kg q12h CrCl 50 – 79: Loading Dose: 5 mg/kg x 1 (max dose: 300 mg); Maintenance Dose: 1.25 – 1.9 mg/kg q12h CrCl 30 – 49: Loading Dose: 5 mg/kg x 1 (max dose: 300 mg); Maintenance Dose: 2.5 mg/kg q24h CrCl < 30: Loading Dose: 5 mg/kg x 1 (max dose: 300 mg); Maintenance Dose: 1.5 mg/kg q36h **Preferred Dosing for Critically Ill Patients** *(Consult ID Pharmacist)* Loading Dose — All CrCl (including HD and CRRT): = 4 x IBW (kg) (max dose: 300 mg) Maintenance Dose: > 90 mL/min: 180 mg q12h 80 – 89 mL/min: 170 mg q12h 70 – 79 mL/min: 150 mg q12h 60 – 69 mL/min: 138 mg q12h 50 – 59 mL/min: 122 mg q12h 40 – 49 mL/min: 110 mg q12h 30 – 39 mL/min: 98 mg q12h 20 – 29 mL/min: 88 mg q12h 10 – 19 mL/min: 80 mg q12h 5 – 9 mL/min: 72 mg q12h 0 mL/min: 65 mg q12h Suggested loading dose and daily doses of colistimethate for desired target colistin Css,avg of 2 mg/L (CID 2017:64. Nation et al)			Loading Dose: 4 x IBW (kg) (max dose: 300 mg) Maintenance Dose: 65 mg q12h; then supplement an additional 40 mg (for a 3-hr IHD session) or 50 mg (for a 4-hr IHD session) post-dialysis alt: 1.5 mg/kg q24h	Loading Dose: 4 x IBW (kg) (max dose: 300 mg) Maintenance Dose: 220 mg q12h alt: 2.5 mg/kg q24h

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https://doi.org/10.1007/s11908-018-0614-0

HEALTHCARE ASSOCIATED INFECTIONS (G BEARMAN AND D MORGAN, SECTION EDITORS)

Pharmacokinetic and Pharmacodynamic Considerations of Antibiotics of Last Resort in Treating Gram-Negative Infections in Adult Critically Ill Patients

Mojdeh S. Heavner[1] · Kimberly C. Claeys[1] · Anne M. Masich[1] · Jeffrey P. Gonzales[1]

Practical Recommendations

Given the current evidence, we recommend loading doses of both colistin and polymyxin B to achieve adequate concentrations. Colistin CL and thus the dosing interval is based on the degree of renal dysfunction and RRT, whereas polymyxin B does not need adjustment in patients with renal dysfunction. In those patients, we recommend polymyxin B dosed on total body weight. Inhaled therapy with colistin is appropriate when treating patients with pneumonia and will optimize the concentrations of the drug in the epithelial lining fluid.

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Use of nebulized antimicrobials for the treatment of respiratory infections in invasively mechanically ventilated adults: a position paper from the European Society of Clinical Microbiology and Infectious Diseases

J. Rello [1, *, 15], C. Solé-Lleonart [2, *, 15], J.-J. Rouby [3], J. Chastre [4], S. Blot [5], G. Poulakou [6], C.-E. Luyt [3], J. Riera [7], L.B. Palmer [8], J.M. Pereira [9, 10], T. Felton [11], J. Dhanani [12], M. Bassetti [13], T. Welte [14], J.A. Roberts [12]

Conclusions

Nebulization of antibiotics in mechanically ventilated adults with respiratory infections is a practice that is increasingly used, despite a lack of standardization and limited evidence on the associated efficacy and safety [2,3]. Based on a previous systematic review and meta-analysis [7], this ESCMID panel does not support the use of nebulization of antibiotics in any of the scenarios assessed because the available evidence is weak and heterogeneous (and in some scenarios entirely absent). Further research to achieve high-quality evidence is urgently needed.

Given that aerosolization of antibiotics is an active area of research, and the literature is emerging [45–47], the meta-analysis should be updated periodically. Hence, these recommendations may change in the future as new study data become available.

Etkinlik /Doğal Direnç

- *P. aeruginosa, A. baumannii*
- *S. maltophilia, Aeromonas* spp
- ***Klebsiella* spp**, *Enterobacter* spp
- *E. coli, Citrobacter* spp
- *Salmonella* spp, *Shigella* spp
- *Legionella* spp.
- *H. influenzae*
- *Bordetella pertussis*
- *M. tuberculosis*
- *Mycobacterium* türlerinin bazıları

- Gram pozitif bakteriler
- *N. meningitidis, N. gonorrhoeae*
- *Proteus mirabilis, M. catarrhalis*
- *Serratia* spp, *M. morganii*
- *Burkholderia* spp.
- *Chromobacterium* spp.
- *Brucella* spp.
- Anaerop bakteriler

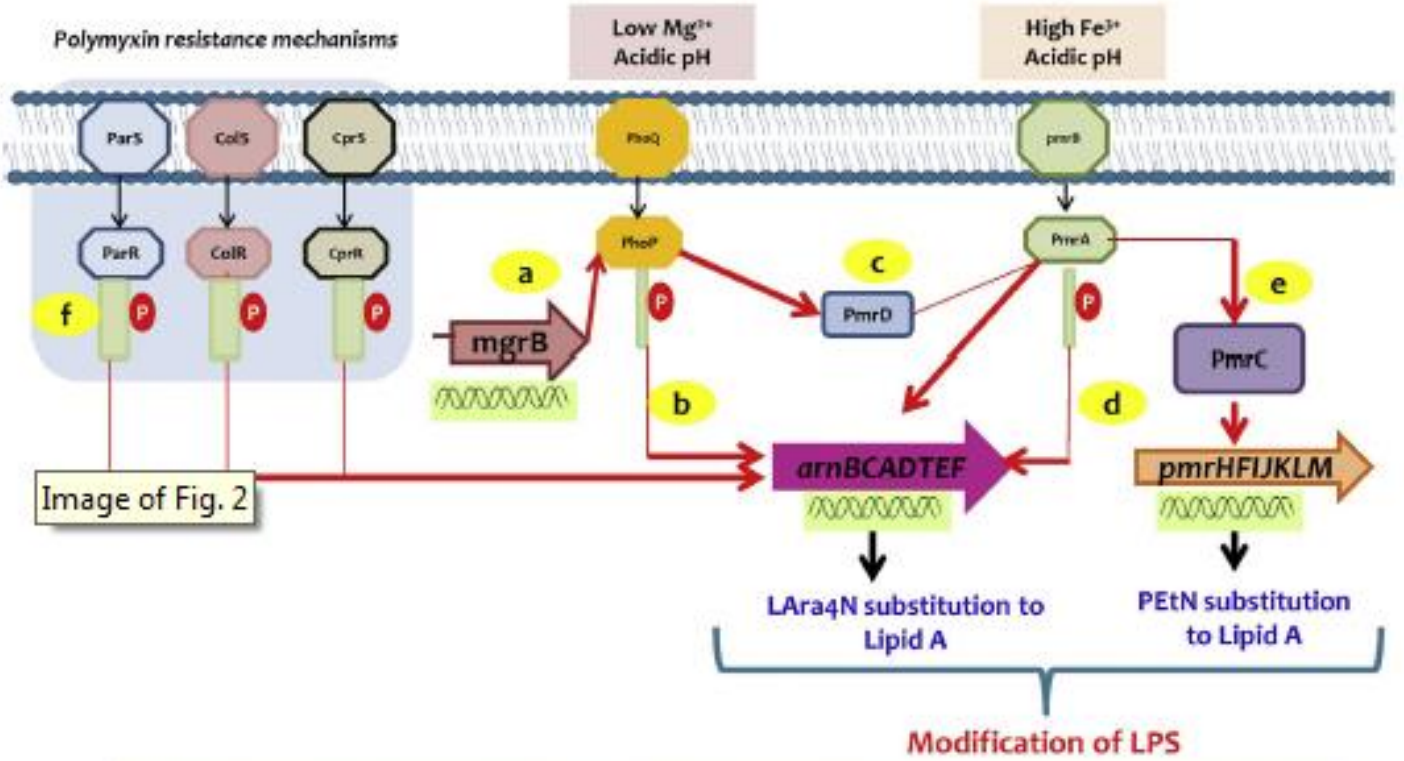
Kazanılmış direnç

- Sonuçta lipid A yapısındaki modifikasyon ile net negatif yükün azalması ile direnç gelişir.

*Lipid A yapısına 4-amino-4-deoksi-L arabinoz (L-ara4N) (yük=0) ya da

** Lipid A yapısına fosfoetanolamin (PEtN) eklenmesi (yük=-1/-1.5)

Kazanılmış Direnç



a) mgrB mediated activation of *arnBCADTEF* for LAra4N substitution
b) direct activation of *arnBCADTEF* operon for LAra4N substitution by phosphorylated phoP
c) pmrD activation by phoP , which activates pmrA for *arnBCADTEF* operon for LAra4N substitution
d) direct activation of *arnBCADTEF* for LAra4N substitution by phosphorylated pmrA
e) PmrA mediated PmrC activation of *pmrHFIJKLM* operon for PEtN substitution
f) ParRS, ColSR, CprRS mediated activation of *arnBCADTEF* for LAra4N substitution (seen only in *P. aeruginosa*)

Kazanılmış direnç

- A.baumannii:

*Lipid A biosentez genlerinin (*lpx*A,C,D)kaybı

(IS *Aba*II)

**Pmr* AB artışı

- P.aeruginosa:

**pmr*AB/*pho*PQ aktivasyonu ile Lipid A yapısının negatif yükünü azaltan ürünler

(*pmr* HIJKLM operonu)

* *cpr*R/*cpr*S

*par*R/*par*S,…

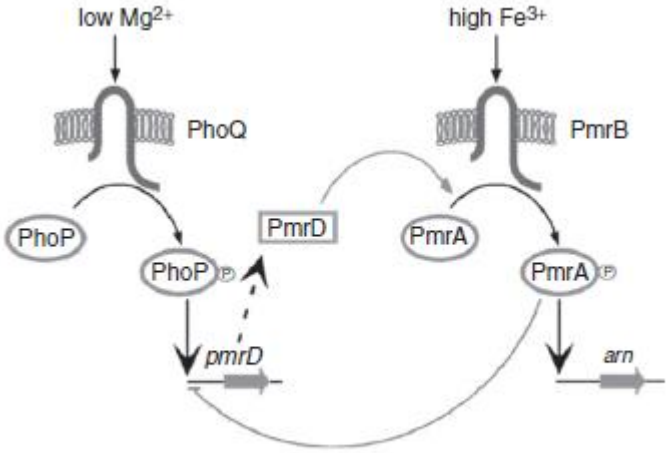


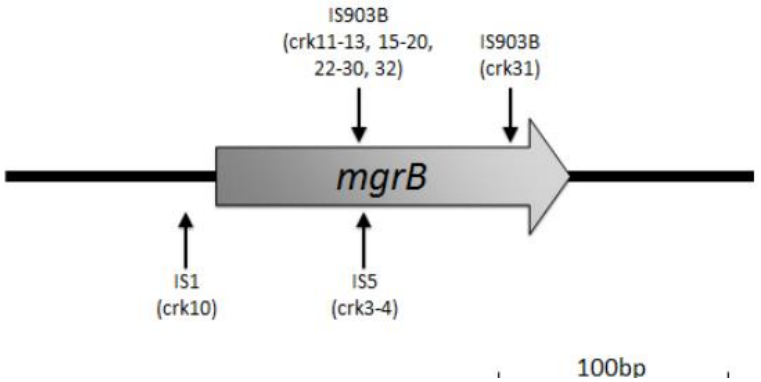
Figure 4. PmrA/PmrB and PhoP/PhoQ two-component regulatory systems.

Kazanılmış direnç

- K.pneumoniae:

*Kolistin etkisi altında iken *mgr*B üzerinden regülatör sistem (*pmr*AB/*pho*PQ)ile LPS modifikasyonu

**OXA-181 geni karbapenemaz ve *mgr*B IS üzerinde yer alır!



- Kapsül üretimi ?
- Pompa sistemleri ?
- Kolistinaz ???

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SCIENTIFIC REPORTS

OPEN

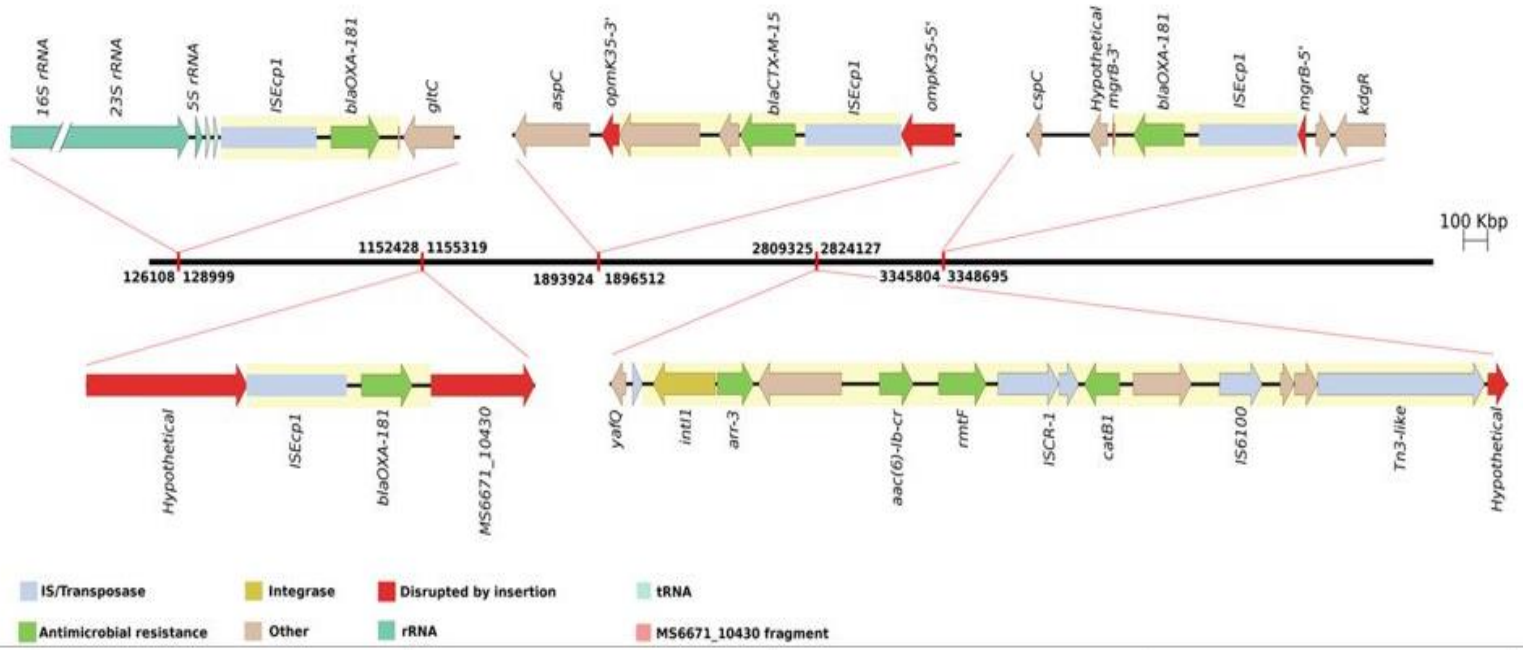
Stepwise evolution of pandrug-resistance in *Klebsiella pneumoniae*

Hosam M. Zowawi[1,2,3,4,*], Brian M. Forde[2,5,*], Mubarak Alfaresi[6], Abdulqadir Alzarouni[7], Yasser Farahat[7], Teik-Min Chong[8], Wai-Fong Yin[8], Kok-Gan Chan[8], Jian Li[9], Mark A. Schembri[2,5], Scott A. Beatson[2,5] & David L. Paterson[1,2]

Received: 07 April 2015

Figure 1 : Diagram of the pandrug-resistant K. *pneumoniae* MS6671 chromosome highlighting the position and context of mobile genetic elements that harbor antimicrobial resistance genes.

From: Stepwise evolution of pandrug-resistance in *Klebsiella pneumoniae*



mcr ile direnç-4’-PEA transferaz

Trends in Microbiology

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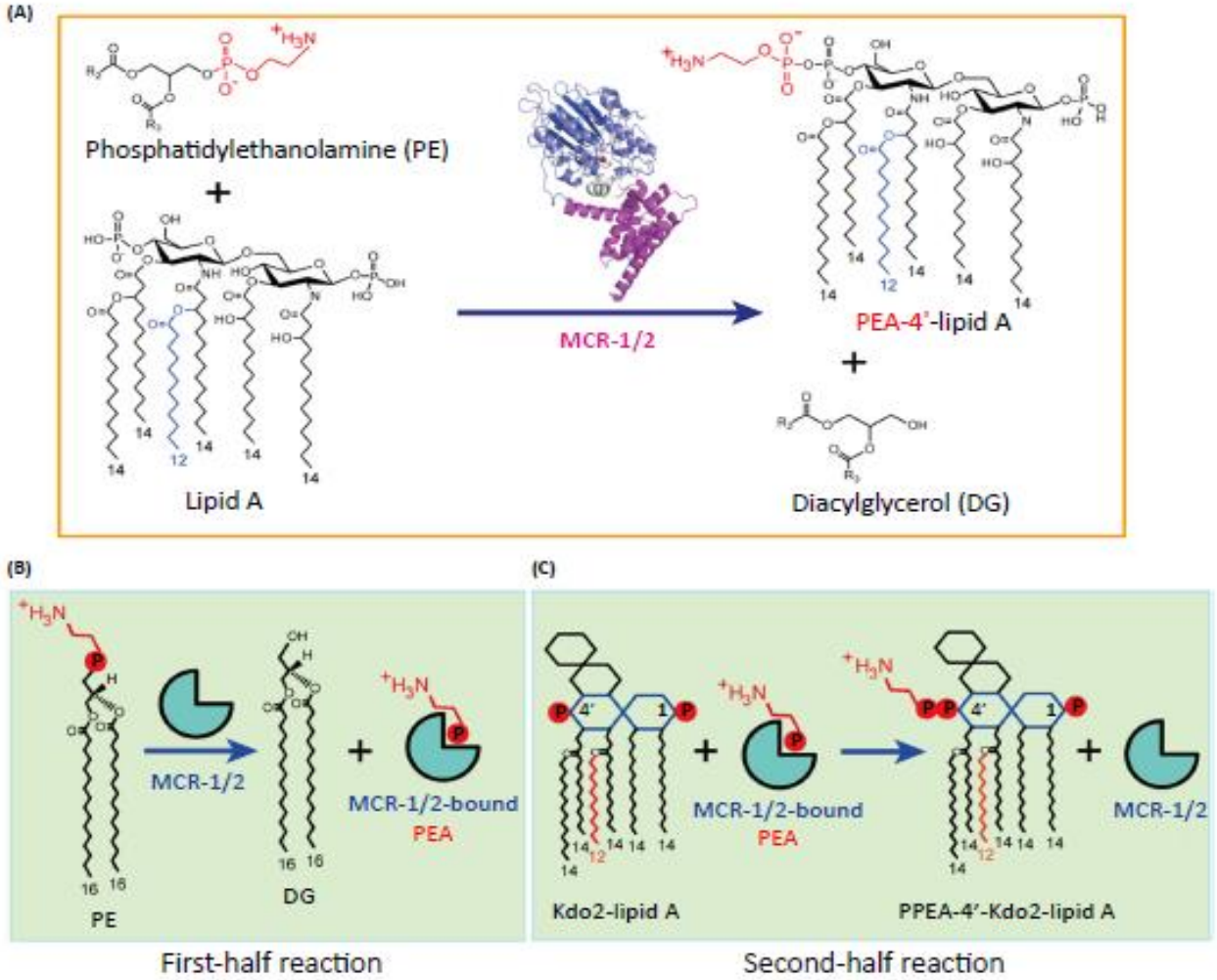
REVIEWS



Direnç tayini

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Recommendations for MIC determination of colistin (polymyxin E) As recommended by the joint CLSI-EUCAST Polymyxin Breakpoints Working Group

Colistin (polymyxin E) MIC determination is associated by several methodological issues. The issues have been extensively investigated by the CLSI-EUCAST joint Polymyxin Breakpoints Working Group and the following method for determination of colistin MIC was agreed:

1. Reference testing of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp. is by the ISO-standard broth microdilution method (20776-1). Note:
   a. Cation-adjusted Mueller-Hinton Broth is used
   b. No additives may be included in any part of the testing process (in particular, no polysorbate-80 or other surfactants)
   c. Trays must be made of plain polystyrene and not treated in any way before use
   d. Sulphate salts of polymyxins must be used (the methanesulfonate derivative of colistin must not be used - it is an inactive pro-drug that breaks down slowly in solution)

2. Susceptibility testing by other methods, including agar dilution, disk diffusion and gradient diffusion, cannot be recommended until historical data have been reviewed or new study data have been generated. Work on these methods is ongoing.

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.

- Mutlaka sıvı mikrodilüsyon !
- Bazı ticari mikrodilüsyon testleri kullanılabilir?
- Gradient test , disk difüzyon ve otomatize sistemler kullanmayın !

Yanlış duyarlı sonuçlar !!!

Direnç tayini-sorunlar ve öneriler

- **Multikompanent karışımlar !**
- **Ürün kompozisyonu değişken**
- **Katyonik içerik**
- **Sürfaktanlar**

- **CA-MH** vs MH
- **Plistren** vs polipropilen, cam
- **Sürfaktansız** vs polisorbat-80 (Tween 80)
- **Kolsitin sülfat** vs CMS

KLİNİK UYUM ?

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Antimicrobial susceptibility testing of colistin – evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

E. Matuschek*, J. Åhman, C. Webster, G. Kahlmeter

EUCAST Development Laboratory, Växjö, Sweden

(n=75) with varying levels of colistin susceptibility was tested.

Results: The colistin BMD products correlated well with reference tests, in particular for Sensititre and the two MICRONAUT products (essential agreement ≥96%: 66/69 (96%, CI 88–99%), 72/75 (96%, CI 88–99%) and 74/75 (99%, CI 92–100%)). The results were somewhat poorer for the BMD products SensiTest and UMIC: EA 88% (51/58, CI 77–95%) and 82% (61/74, CI 72–89%), respectively), and considerably poorer for the gradient tests (EA 43–71% depending on gradient test and Mueller-Hinton agar manufacturer). The gradient tests generally underestimated colistin MICs, resulting in a significant number of false susceptible results (9–18 of total 75 tests, compared with 1–3 for the BMD products).

Conclusions: Based on the results of this study, we advise laboratories not to trust gradient tests for colistin susceptibility testing and to use broth microdilution methods for this purpose. There are several commercial broth microdilution tests available and in principle they perform well. **E. Matuschek, Clin Microbiol Infect 2018;24:865**

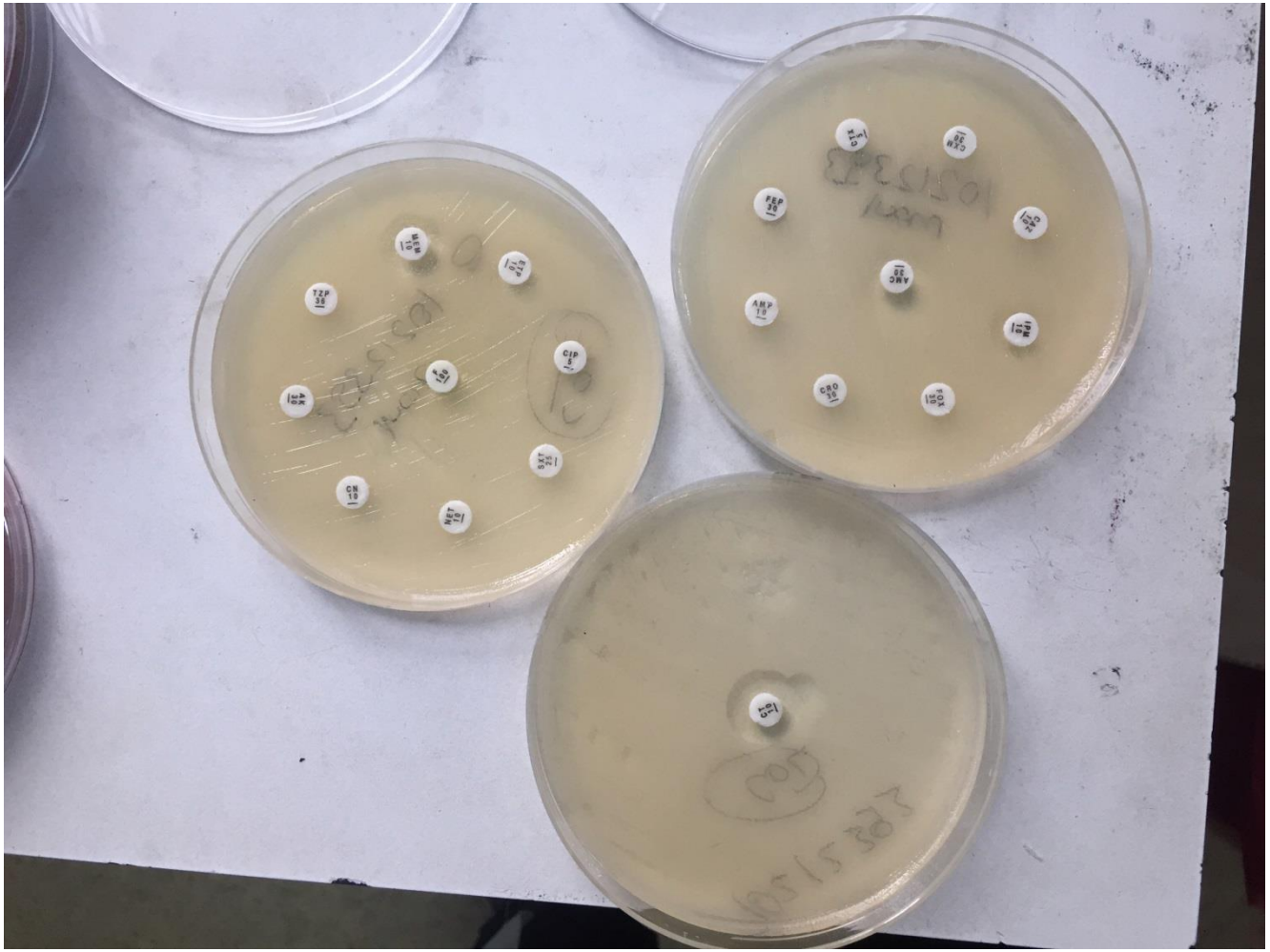
Kolistin direnç tayini…

- Kapiller elektroforez
- Micromax assay (A.baumannii)
- **Rapid Polimyxine NP test (hızlı, yüksek duyarlılık ve özgüllük)**
- Seçici besiyerleri (Super Polymyxine medium)
- ….

Gerçek hayat-olasılıklar

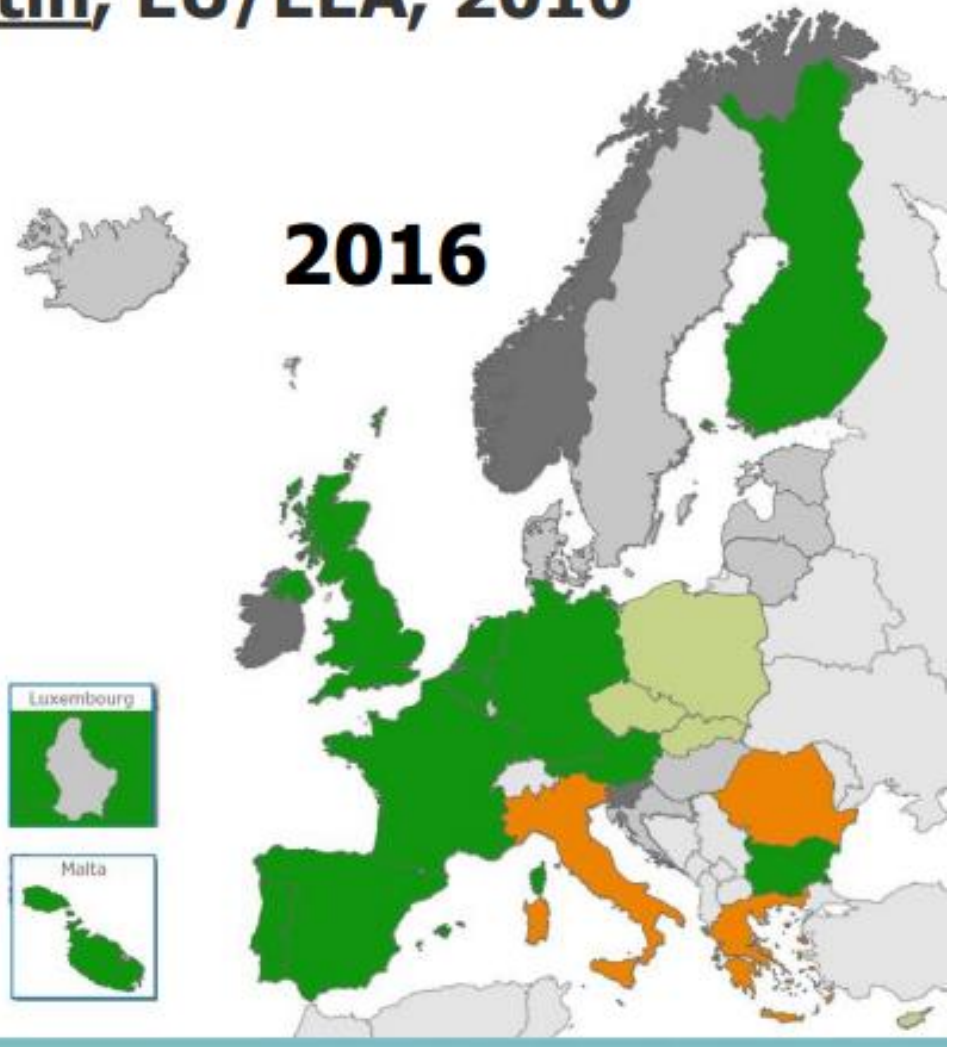
- BMD, Sensititre ya da Micronaut ile sonuç !
- Kolistin duyarlılığı yapamıyoruz!
- Dirençli sonucu bildir (OS, G-test, DD) duyarlı çıkarsa sonuç yazma !
- DD, OS ya da DD ile sonucu yaz, metodu yaz yorumsuz olarak bildir?

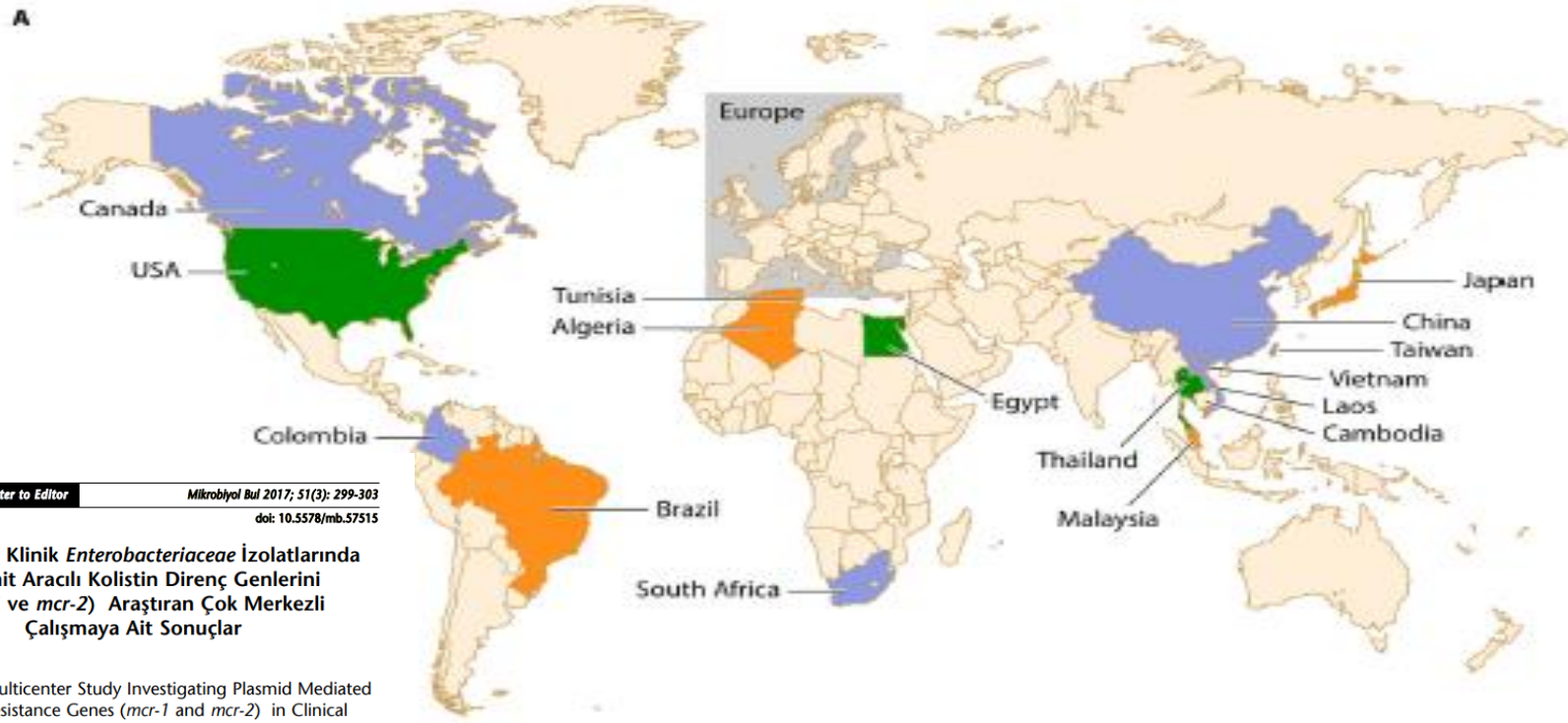
Gerçek hayat



Klebsiella pneumoniae: % of invasive isolates with combined resistance to carbapenems and colistin, EU/EEA, 2016

- < 1%
- 1% to <5%
- 5% to <10%
- 10% to <25%
- 25% to <50%
- ≥ 50 %
- Less than 10 isolates reported
- No data

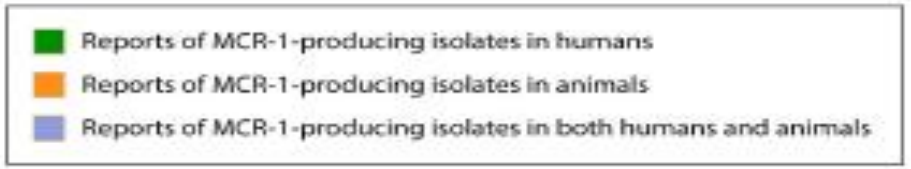




Editöre Mektup/Letter to Editor
Mikrobiyol Bul 2017; 51(3): 299-303
doi: 10.5578/mb.57515

Ülkemizde Klinik *Enterobacteriaceae* İzolatlarında Plazmit Aracılı Kolistin Direnç Genlerini (*mcr-1* ve *mcr-2*) Araştıran Çok Merkezli Çalışmaya Ait Sonuçlar

Results of a Multicenter Study Investigating Plasmid Mediated Colistin Resistance Genes (*mcr-1* and *mcr-2*) in Clinical *Enterobacteriaceae* Isolates from Turkey



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Letter to the Editor

First report of *Escherichia coli* carrying the mobile colistin resistance gene *mcr-1* in Turkey

in all three strains and showed 100% nucleotide similarity with the previously annotated mcr-1 gene [2]. Plasmid sequencing of three strains (A1, A5 and A9) resulted in long contigs of multiple

FIG 4 Reports of MCR-1-producing isolates in humans, animals, and both humans and animals.

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. Demiroglu [g], H.E. Alışkan [h], O. Memikoglu [c], Ş. Menekşe [i], Ş. Kaya [j], N.A. Demir [k], I. Karaoglan [l], S. Başaran [m], Ç. Hatipoglu [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. Mülazımoglu [d], O. Ural [k], F. Can [v], H. Akalın [o], Turkish Society of Clinical Microbiology and Infectious Diseases, Healthcare-related Infections Study Group, Turkey

SUMMARY

This article describes the emergence of resistance and predictors of fatality for 1556 cases of healthcare-associated Gram-negative bloodstream infection in 2014 and 2015. The colistin resistance rate in *Klebsiella pneumoniae* was 16.1%, compared with 6% in 2013. In total, 660 (42.4%) cases were fatal. The highest fatality rate was among patients with *Acinetobacter baumannii* bacteraemia (58%), followed by *Pseudomonas aeruginosa* (45%), *Klebsiella pneumoniae* (41%), *Enterobacter cloacae* (32%) and *Escherichia coli* (28%). On multi-variate analysis, the minimum inhibitory concentrations for carbapenems [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01–1.04; $P = 0.002$] and colistin (OR 1.1, 95% CI 1.03–1.17; $P = 0.001$) were found to be significantly associated with fatality.

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Risk Faktörleri

- Kolistin kullanımı
  - Kolistin dirençli bakteri ile kolonizasyon veya infeksiyon

Kontopidou F. ve ark.,Clin Microbiol İnfec 2009

Matthaiou DK ve ark. ,Crit Care Med 2000

- Sub-optimal doz veya uzamış monoterapi tedavi

Poudyal A ve ark., JAC 2008

- Digestive sistem selektif dekontaminasyonu

Teysir Halaby et al., Antimicrob. Agents Chemother 2013

Beklenen Olasılıklar !

Microb Drug Resist. 2018 Sep;24(7):966-972. doi: 10.1089/mdr.2017.0173. Epub 2017 Dec 21.

Hospital Outbreak of a Colistin-Resistant, NDM-1- and OXA-48-Producing Klebsiella pneumoniae: High Mortality from Pandrug Resistance.

Guducuoglu H[1], Gursoy NC[2], Yakupogullari Y[2], Parlak M[1], Karasin G[1], Sunnetcioglu M[3], Otlu B[2].

Author information

Abstract

Colistin resistance causes substantial problems in the treatment of serious infections with carbapenem-resistant (CR) gram-negative bacteria. In this study, we report a fatal hospital outbreak from the spread of a pandrug-resistant Klebsiella pneumoniae clone. An outbreak investigation was conducted after consecutive isolation of nine CR-K. pneumoniae (CR-Kp) strains from eight patients in two intensive care units of a university hospital within 2 weeks. Carbapenem and colistin resistance genes were investigated with PCR, clonal relationships of isolates were studied with pulse-field gel electrophoresis, and multilocus sequence types were determined. The outcomes of the affected patients were analyzed. Genotyping showed a predominant CR-Kp clone consisting of seven strains from six patients. These strains were in ST11 type, an international high-risk clone. They were resistant to all antimicrobials, including colistin, and positive for NDM-1 and OXA-48 carbapenemases, but negative for plasmid-borne colistin resistance genes. One patient had colonization and the remaining five died due to the infection within mean 12 days. No environmental or staff links could be established, and the outbreak was stopped by augmenting infection-control measures. Colistin-resistant K. pneumoniae could clonally expand in the hospital setting, and this spread might be associated with high mortality due to the lack of an appropriate treatment option. Immediate implementation of infection-control measures may be the best way to limit fatal consequences of the spread of such incurable pathogens.

Heteroresistans ?

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]

Kombinasyonlar ?

- Dama Tahtası Yöntemi (Checker Board Test)
- Zamana Bağlı Öldürme Yöntemi (Time Kill Assay)
- Gradient test (E-test)

Çelişkili sonuçlar !

Klinik yansıma ?

KOMBİNASYON!

Table 3. Results of in vitro studies carried out for synergy in combination of drugs with polymyxins.

Study (year)	Organism (n)	Polymyxin studied	Method	Drug combined	Synergy	Ref.
Lim et al. (2011)	*A. baumannii* (31)	PMB	Time-kill study	Rifampicin	41.9	
				Tigecycline	29	
Liang et al. (2011)	*A. baumannii* (14)	Colistin	Time-kill study	Meropenem	100	[168]
				Minocycline	100	
				Rifampicin	100	
Sheng et al. (2011)	*Acinetobacter* spp. (17)	Colistin	Time-kill study	Imipenem	75–100	[171]
			Checkerboard	Imipenem	42–100	
Wareham et al. (2011)	*A. baumannii* (6)	Colistin	Time-kill study	Teichoplanin	100	[178]
			Checkerboard	Teichoplanin	100	
Souli et al. (2011)	*K. pneumonia* (17)	Colistin	Time-kill study	Fosfomycin	11.8	[216]
Gordon et al. (2010)	*A. baumannii* (39)	Colistin	Etest	Vancomycin	100	[156]
Elemam et al. (2010)	*K. pneumonia* (12)	PMB	Checkerboard	Rifampicin	100	[162]
				Doxycycline	100	
				Tigecycline	100	
Pankey et al. (2010)	*A. baumannii* (8)	PMB	Time-kill study	Meropenem	100	[217]
			Etest	Meropenem	63	
Principe et al. (2009)	*A. baumannii* (22)	Colistin	Checkerboard	Tigecycline	8.3	[218]
Lopez et al. (2008)	*P. aeruginosa* (12)	Colistin	Checkerboard	Doxycycline	66.6	[219]
				Rifampicin	16.6	
				Azithromycin	25	
Tan et al. (2007)	*A. baumannii* (13)	Colistin	Time-kill study	Minocycline	92	[220]
Li et al. (2007)	*A. baumannii* (8)	Colistin	Checkerboard	Rifampicin	100	[169]
Timurkaynak et al. (2006)	*P. aeruginosa* (5)	Colistin	Checkerboard	Rifampicin	40	[221]
				Meropenem	0	
				Azithromycin	0	
Timurkaynak et al. (2006)	*A. baumannii* (5)	Colistin	Checkerboard	Rifampicin	80	[221]
				Meropenem	60	
				Azithromycin	60	
Bolmstrom et al. (2005)	*A. baumannii* (6)	Colistin	Checkerboard	Rifampicin	100	[176]
Landman et al. (2005)	*P. aeruginosa* (10)	PMB	Time-kill study	Rifampicin	90	[222]
				Imipenem	80	
				Azithromycin	40	
			Checkerboard	Rifampicin	14	[223]
			Time-kill study	Ceftazidime	100	[87]
				Ciprofloxacin	0	
			Checkerboard	Rifampicin	85	[169]

Colistin: An update on the antibiotic of the 21st Century

Article *in* Expert Review of Anti-infective Therapy · August 2012

DOI: 10.1586/eri.12.78 · Source: PubMed

Journal of
Clinical Medicine

MDPI

Article

Intravenous Colistin Monotherapy versus Combination Therapy against Carbapenem-Resistant Gram-Negative Bacteria Infections: Meta-Analysis of Randomized Controlled Trials

I-Ling Cheng [1], Yu-Hung Chen [1], Chih-Cheng Lai [2] and Hung-Jen Tang [3,*]

Table 1. Characteristics of included studies.

Author/Publication Year	Study Year	Study Site	Bacteria	Polymicrobial	Setting	Infection Type (%)	Usage of IV Colistin Dose	No. of Polymyxin	No. of Combination with
Aydemir, 2013	2011–2012	Turkey	Carbapenem-resistant *A. baumannii*	No	ICU	VAP (100)	300 mg colistin based activity/day, t.i.d. (9 MIU per day)	Colistin (22)	Rifampicin (21)
Durante-Mangoni, 2013	2010–2011	Italy	Extensive-drug resistant *A. baumannii*	Yes	ICU	VAP (69), BSI (20), HAP (9), cIAI (2)	2 MIU every 8 h	Colistin (105)	Rifampicin (104)
Sirijatuphat, 2014	2010–2011	Thailand	Carbapenem-resistant *A. baumannii*	Yes	ICU and ward	Pneumonia (76.6), BSI (5.4), UTI (5.4), IAI (6.4), SSTI (3.2), CNSI (1.0), other (2.1)	5 mg colistin based activity/kg/day (9 MIU per day)	Colistin (47)	Fosfomycin (47)
Paul, 2018	2013–2016	Israel, Greece, Italy	Carbapenem-resistant gram-negative bacteria, including *A. baumannii*, Enterobacteriaceae, Pseudomonas, and others	No	ICU and ward	VAP/HAP (44.8), BSI (42.6), UTI (6.4), pVAP (6.2)	9 MIU loading, followed by 4.5 MIU every 12 h	Colistin (198)	Meropenem (208)
Makris, 2018	-	Greece	Carbapenem-resistant *A. baumannii*	No	ICU	VAP (100)	3 MIU t.i.d.	Colistin (19)	Ampicillin-sulbactam (20)

Abbreviations: IV, intravenous; ICU, intensive care unit; MIU, million international units; VAP, ventilator-associated pneumonia; BSI; bloodstream infection; HAP, hospital-acquired pneumonia; cIAI, complicated intra-abdominal infection; UTI, urinary tract infection; SSTI, skin and soft tissue infection; CNSI, central nervous system infection; t.i.d, three times per day.

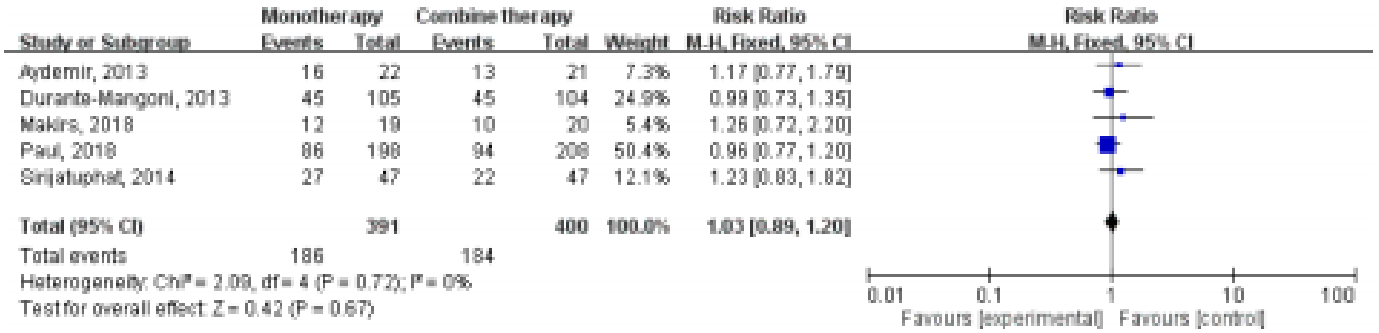


Figure 4. Colistin monotherapy versus colistin-based combination therapy, all-cause mortality. M-H, Mantel-Haenszel.

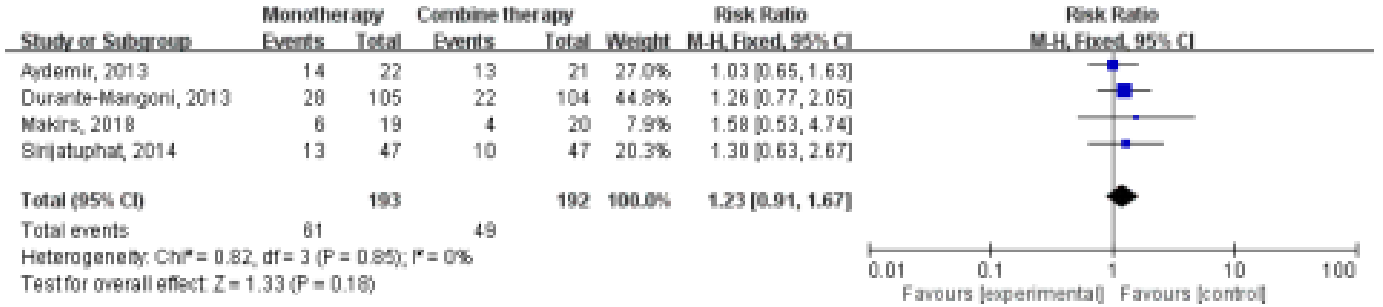


Figure 5. Colistin monotherapy versus colistin-based combination therapy, infection-related mortality. M-H, Mantel-Haenszel.

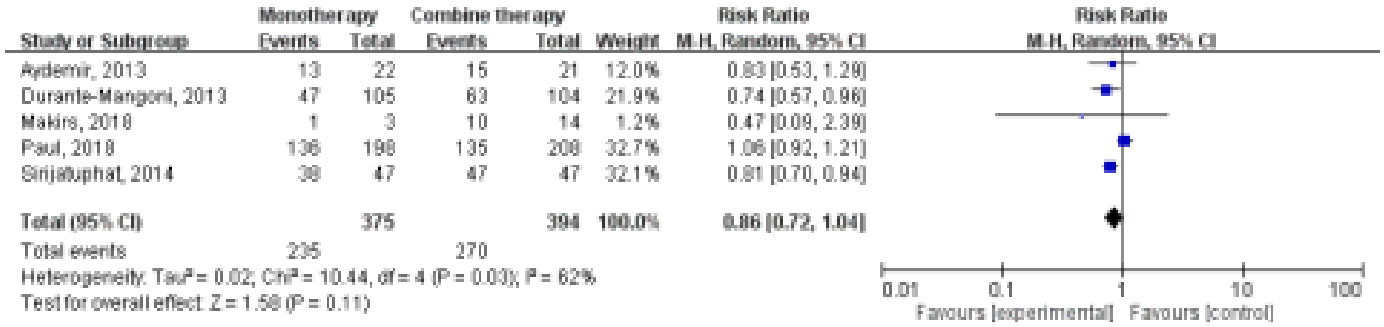


Figure 6. Colistin monotherapy versus colistin-based combination therapy, microbiologic response.

Acinetobacter baumannii - KDE

- Kolistin kombinasyonu monoterapiye göre-
  Anlamlı yüksek eradikasyon -
  Nisbeten yüksek sağkalım(14.gün)

- Sulbaktam ve karbapenemli kombinasyonlar arasında fark yok

Batirel A et al. Eur J Clin Microbiol Infect Dis 2014

ACCEPTED MANUSCRIPT

Treatment outcomes of colistin and carbapenem-resistant *Acinetobacter baumannii* infections: an exploratory subgroup analysis of a randomized clinical trial

Yaakov Dickstein ✉, Jonathan Lellouche, Maayan Ben Dalak Amar, David Schwartz, Amir Nutman, Vered Daitch, Dafna Yahav, Leonard Leibovici, Anna Skiada, Anastasia Antoniadou, ... Show more

Clinical Infectious Diseases, ciy988, https://doi.org/10.1093/cid/ciy988

Published: 20 November 2018 **Article history** ▾

Conclusions

Colistin resistance as determined by BMD was associated with significantly lower mortality among patients with severe CRAB infections. Among patients with CoR isolates, colistin monotherapy was associated with a better outcome compared to colistin-meropenem combination therapy.

Toksisite

NEFROTOKSİSİTE :

- 2011 yılında meta-analiz: %0-53.3
- Genellikle ilk 5-7 gün içinde
- Geriye dönebilen

Javan AO et al. Eur J Clin Pharmacol 2015

NÖROTOKSİSİTE

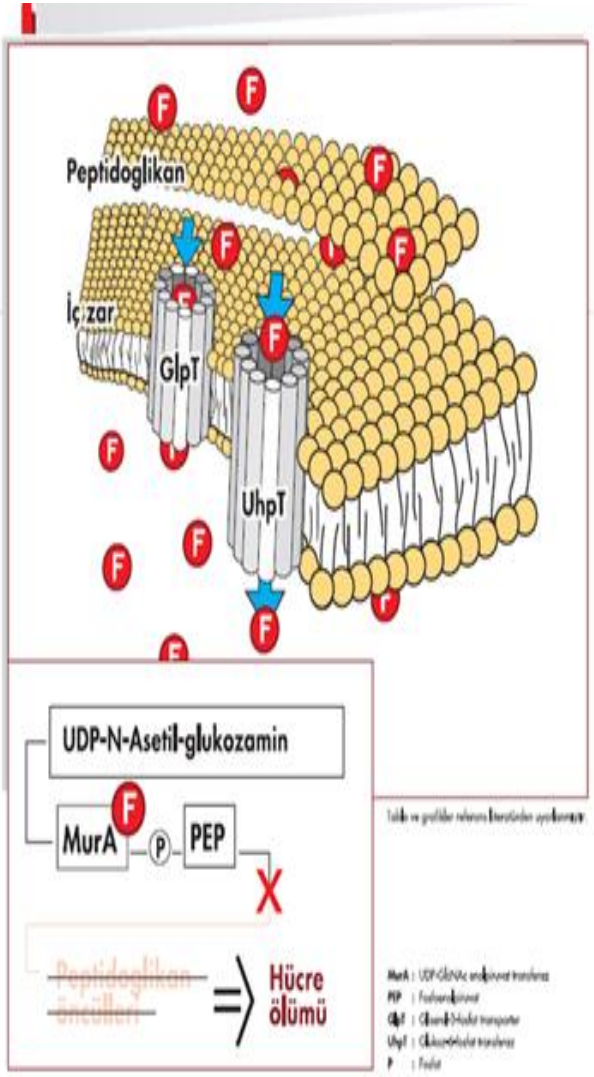
- Parestezi(İV:%7.3, İM:%27)
- Konfüzyon
- Vertigo
- Ataksi
- Konvülsiyon
- Nöromuskuler blok ve apne
- Doza bağımlı ve geriye dönebilen

Gregoire G et al. Clin Pharmacokinetic 2017

Kolistin kullanımı

- İn-vitro sonuçlar !!!
- Rutin kullanımdan mümkün olduğunca kaçınalım !
- Monoterapi A.baumannii için uygun diğerlerinde kombinasyon !
- İnhalasyon yolu ile kullanım ??? (belki KF,..vb)

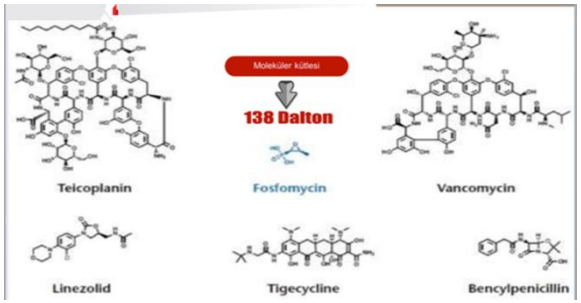
Fosfomisin



Fosfomisin, MurA (UDP-NAG enol piruviltransferaz) inhibitörüdür. Bu sayede **bakteri hücre duvarı** (peptidoglikan) **sentezini ilk basamağında inhibe eder ve bakterisid etki** gösterir.

Dokulara iyi dağılım

İdrarla atılım



Castenada – Garcia et al. Antibiotics 2013, 2, 217- 236

Fosfomisin

Duyarlı mikroorganizmalar	Potansiyel direnç gelişme riski olan duyarlı mikroorganizmalar	İntrensek dirençli mikroorganizmalar
Gram-pozitifler	**Gram-pozitifler**	
Staphylococcus aureus (MS, MR)	*Enterococcus faecalis*	
Streptococcus pyogenes	*Staphylococcus epidermidis*	
Streptococcus pneumoniae (PR+/-)		
Gram-negatifler	**Gram-negatifler**	**Gram-negatifler**
Citrobacter spp.	*Enterobacter cloacae*	*Acinetobacter* spp.
Edwardsiella spp.	*Klebsiella pneumoniae*	*Burkholderia cepacia*
Escherichia coli	*Proteus inconstans*	*Morganella morganii*
Haemophilus influenzae	*Pseudomonas aeruginosa*	*Stenotrophomonas maltophilia*
Klebsiella oxytoca	*Serratia marcescens*	
Neisseria spp.		
Proteus mirabilis		
Providencia rettgeri		
Anaeroplar		**Anaeroplar**
Peptococcus spp.		*Bacteroides* spp.
Peptostreptococcus spp.		

MS: Metisiline duyarlı, MR: Metisiline dirençli, PR+: Penisiline dirençli, PR-: Penisiline duyarlı.

Fosfomisin duyarlılık

- E.coli dışında Agar Dilüsyon !

Enterobacteriaceae (new taxonomy: Enterobacterales*)

EUCAST Clinical Breakpoint Tables v. 8.0, valid from 2018-01-01

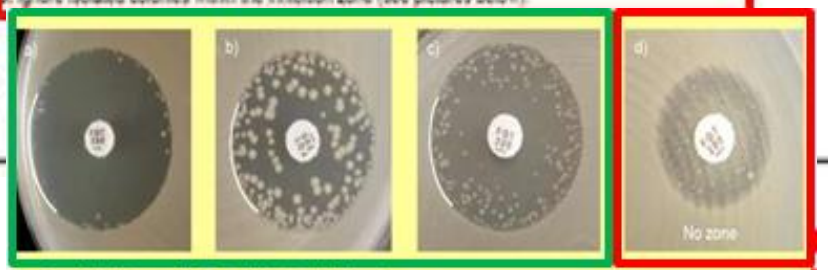
Miscellaneous agents	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Chloramphenicol	8	8	30	17	17
Colistin[1]	2	2		Note[A]	Note[A]
Dapotomycin	-	-		-	-
Fosfomycin iv	32[2]	32[2]	200[B]	24[C,D]	24[C,D]
Fosfomycin oral (uncomplicated UTI only)	32[2]	32[2]	200[B]	24[C,D]	24[C,D]
Fusidic acid	-	-		-	-
Metronidazole	-	-		-	-
Nitrofurantoin (uncomplicated UTI only), *E. coli*	64	64	100	11	11
Nitroxoline (uncomplicated UTI only), *E. coli*	16	16	30	15	15
Rifampicin	-	-		-	-
Spectinomycin	-	-		-	-
Trimethoprim (uncomplicated UTI only)	2	4	5	18	15
Trimethoprim-sulfamethoxazole[3]	2	4	1.25-23.75	14	11

Notes

Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

1. Colistin MIC determination should be performed with broth microdilution. Quality control must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr-1* positive).
2. Agar dilution is the reference method for fosfomycin. MICs must be determined in the presence of glucose-6-phosphate (25 mg/L in the medium). Follow the manufacturers' instructions for commercial systems.
3. Trimethoprim:sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as the trimethoprim concentration.

A. Use an MIC method (broth microdilution only).
B. Fosfomycin 200 µg disks must contain 50 µg glucose-6-phosphate.
C. Zone diameter breakpoints apply to *E. coli* only. For other Enterobacteriaceae, use an MIC method.
D. Ignore isolated colonies within the inhibition zone (see pictures below).



Examples of inhibition zones for *Escherichia coli* with fosfomycin.
a-c) Ignore all colonies and read the outer zone edge.
d) Record as no inhibition zone.

In Vitro Activity of Fosfomycin against *Escherichia coli* Isolated from Patients with Urinary Tract Infections in Canada as Part of the CANWARD Surveillance Study

TABLE 1 *In vitro* activities of orally available antimicrobial agents against 868 urinary isolates of *E. coli* isolated by clinical laboratories across Canada from 2010 to 2013

E. coli isolate phenotype(s) (no. of isolates) and antimicrobial agent	MIC_{50}[e]	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
All (868)						
Fosfomycin	≤1	4	≤1–512	99.4	0.5	0.1
SXT	≤0.12	>8	≤0.12–>8	74.7		25.3
Nitrofurantoin	16	32	≤1–512	96.1	2.4	1.5
Ciprofloxacin	≤0.06	>16	≤0.06–>16	77.4	0.1	22.5
Amoxicillin-clavulanate	4	16	0.5–>32	81.3	13.0	5.7

RESEARCH ARTICLE

Antimicrobial Susceptibility and Molecular Mechanisms of Fosfomycin Resistance in Clinical *Escherichia coli* Isolates in Mainland China

Ya Li[1], Bo Zheng[1]*, Yun Li[1], Sainan Zhu[2], Feng Xue[1], Jian Liu[1]

Sample source	No. of isolates	ESBL (%)	No. of isolates inhibited at fosfomycin MIC (mg/L) of														MIC_{50}(mg/L)	MIC_{90}(mg/L)	S (%)	I (%)	R (%)
			0.062	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	>256					
urine	262	65.9	7	59	116	34	15	4	4	1	4	4	1	3	8	2	0.25	4	95.0	1.2	3.8
sputum	264	77.9	7	47	94	27	23	9	10	5	2	2	4	15	12	7	0.25	128	87.1	5.7	7.2
blood	343	67.9	6	72	135	59	14	9	9	5	6	2	3	7	9	7	0.25	16	93.3	2.0	4.7
pus	240	63.3	5	46	90	38	19	5	4	3	3	6	5	10	3	3	0.25	32	93.3	4.2	2.5
Total	1109	68.8	25	224	435	158	71	27	27	14	15	14	13	35	32	19	0.25	32	92.2	3.2	4.6

Antimicrobial Susceptibilities of Commonly Encountered Bacterial Isolates to Fosfomycin Determined by Agar Dilution and Disk Diffusion Methods[▽]

Ching-Lan Lu,[1,2] Chia-Ying Liu,[4] Yu-Tsung Huang,[2,3,4] Chun-Hsing Liao,[4] Lee-Jene Teng,[3,5] John D. Turnidge,[6,7] and Po-Ren Hsueh[2,3]*

Species	Subgroup[a]	No. of isolates with the following MIC (μg/ml):														ECV[b] (μg/ml)	% isolates with MICless than or equal to current breakpoint[c]	
		Total	0.25	0.5	1	2	4	8	16	32	64	128	256	512	>512		CLSI	EUCAST
Escherichia coli		100	15	70	6	5	2		2							1	100	100
Klebsiella pneumoniae		100			1		12	45	19	8	7	2	5		1	16	92	85

Antimicrob Agents Chemother 2014;58:1252–1256

Fosfomisin

- KDE olgularda dağılım

Biomedical Research 2017; 28 (8): 3731-3735

ISSN 0970-938X
www.biomedres.info

Determination of MIC distribution of colistin, fosfomycin, and tigecyclin antibiotics against carbapenem resistant enterobacteriaceae.

Serap Süzük[1*], Banu Kaşkatepe[2], Havva Avcıküçük[3]

Table 3. Determination of the MIC values antibiotics tested for isolates (n=63).

Bacteria	Colistin		Fosfomycin		Tigecycline	
	S (%)	R (%)	S (%)	R (%)	S (%)	R (%)
K. pneumoniae	58 (96.67)	2 (3.33)	38 (63.33)	22 (36.67)	43 (71.67)	17 (28.33)
E. coli	2 (100.00)	0.00	2 (100.00)	0.00	2 (100.00)	0.00
Enterobacter cloace	1 (100.00)	0.00	0.00	1 (100.00)	0.00	1 (100.00)
Total	61 (96.83)	2 (3.17)	40 (63.49)	23 (36.51)	45 (71.43)	18 (28.57)

Fosfomisin PK/PD

Current Infectious Disease Reports (2018) 20: 10
https://doi.org/10.1007/s11908-018-0614-0

HEALTHCARE ASSOCIATED INFECTIONS (G BEARMAN AND D MORGAN, SECTION EDITORS)

CrossMark

Pharmacokinetic and Pharmacodynamic Considerations of Antibiotics of Last Resort in Treating Gram-Negative Infections in Adult Critically Ill Patients

Mojdeh S. Heavner[1] · Kimberly C. Claeys[1] · Anne M. Masich[1] · Jeffrey P. Gonzales[1]

Practical Recommendations

Based on the available evidence, fosfomycin IV is a reasonable option in combination therapy for severe systemic infections with resistant organisms [90•]. We recommend a loading dose of fosfomycin in critically ill patients, higher maintenance doses in the first 24–48 h, followed by frequent but lower doses based on estimated of CrCL using urinary creatinine collection.

- Sistemik olgularda Fosfomisin tromethamine ? (0.53 g fosfomisin/1 g)

Fosfomisin

- Dirençli bakterilerde kombinasyon ile
- Üriner infeksiyonlar başta olmak üzere monoterapi??

BMJ Open. 2015; 5(3): e007363.
Published online 2015 Mar 31. doi: [10.1136/bmjopen-2014-007363]
PMCID: PMC4386243
PMID: 25829373

Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* (FOREST): study protocol for an investigator-driven randomised controlled trial

Clara Rosso-Fernández,[1,2] Jesús Sojo-Dorado,[3] Angel Barriga,[1] Lucía Lavín-Alconero,[1] Zaira Palacios,[3,4] Inmaculada López-Hernández,[3] Vicente Merino,[5] Manuel Camean,[5] Alvaro Pascual,[3,6] Jesús Rodríguez-Baño,[3,7] and and the FOREST Study Group

Tigesiklin PK/PD

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https://doi.org/10.1007/s11908-018-0614-0

HEALTHCARE ASSOCIATED INFECTIONS (G BEARMAN AND D MORGAN, SECTION EDITORS)

Pharmacokinetic and Pharmacodynamic Considerations of Antibiotics of Last Resort in Treating Gram-Negative Infections in Adult Critically Ill Patients

Mojdeh S. Heavner[1] · Kimberly C. Claeys[1] · Anne M. Masich[1] · Jeffrey P. Gonzales[1]

Practical Recommendations

Tigecycline remains used in clinical practice secondary to its broad spectrum of activity, including many multidrug-resistant gram-negative organisms. This is in spite of a black box warning associating tigecycline use with increased all-cause mortality [70]. To help decrease the risk of clinical failure, investigators have studied tigecycline use in doses higher than that recommended by the package insert (100 mg every 12 h) as well as in combination therapy with numerous other antibiotic therapies. We recommend to limit use to combination therapy and consider higher doses, especially for infections such as lower respiratory tract infections where tigecycline has suboptimal PK.

Tigesiklin

- Karıniçi ve Deri-Yumuşak Doku bakteriyemik/septik şok olmayan olgularda tedavi seçeneği !
- Diğer klinik durumlarda (HAP,VİP,…) uygun olmayabilir!
- Kombinasyon ve yüksek doz (2x100mg)!

  En son seçenek olabilir!

Clinical Microbiology and Infection 23 (2017) 704–712

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

New agents for the treatment of infections with Gram-negative bacteria: restoring the miracle or false dawn?

H. Wright [1], R.A. Bonomo [2], D.L. Paterson [1,*]

- **Ceftazidim/Avibactam**
- Meropenem/Vaborbactam
- İmipenem /Relebactam
- Aztreonam/Avibactam
- …
- Cefideracol
- Ceftolozane/tazobactam

- Plazomisin

- Eravacycline

As new agents emerge and are used in clinical practice, history would suggest that pathogenic bacteria will continue to evolve in response to this selection pressure. Early reports of resistance to ceftazidime/avibactam after clinical use highlight this possibility and careful monitoring for development and spread of resistance to any new agents is vital. The history of antibiotic use to date continues to suggest that use leads to resistance, as such additional focus on appropriate stewardship practices are vital in maximizing the efficacy and longevity of any new agents that enter clinical practice. The interval between the discovery of a new agent and reports of clinical resistance appear disappointingly brief. Further work on rapid diagnostic techniques that allow targeted therapy may not only lead to better therapeutic outcomes for patients but also assist in preserving the utility of both old and new agents.

Brief Communication

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, V. Ramasubramanian

Department of Infectious Diseases, Apollo Hospitals, Chennai, Tamil Nadu, India

Abstract

Background: As the use of colistin to treat carbapenem-resistant Gran increasingly reported in Indian hospitals. **Materials and Methods:** Ret colistin-resistant isolates (minimum inhibitory concentration >2 mcg/ml). treatment were analyzed. **Results:** Twenty-four colistin-resistant isolates A history of previous hospitalization within 3 months was present in all the Urine was the most common source of the isolate, followed by blood and r of all isolates. Sixteen (66.6%) were considered to have true infection, whe Susceptibility of these isolates to other drugs tested was tigecycline in 75% 12.5%, and fosfomycin (sensitive in all 4 isolates tested). Antibiotics that we antimicrobials-tigecycline, chloramphenicol, fosfomycin, amikacin, ciprofl who were considered to have colonization, there were no deaths. Bacteren to all nonbacteremic patients ($P = 0.014$). **Conclusions:** Colistin resistanc is emerging in Indian hospitals. At least one-third of isolates represented c treatment. Among patients with true infection, only 25% had a satisfactory outcome and survived to discharge. Fosfomycin, tigecycline, and chloramphenicol may be options for combination therapy.

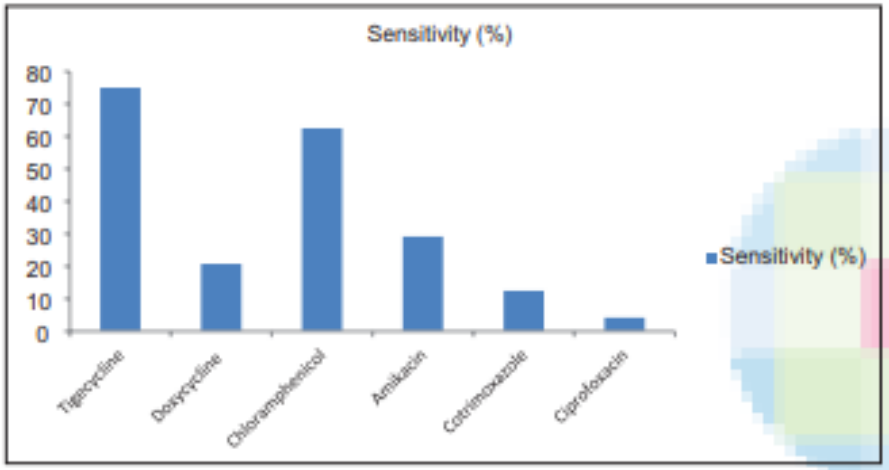

Figure 2: Sensitivity of the colistin-resistant isolates to other drugs tested

Eur J Clin Microbiol Infect Dis (2010) 29:301–305
DOI 10.1007/s10096-009-0857-7

ARTICLE

Infections by pandrug-resistant gram-negative bacteria: clinical profile, therapeutic management, and outcome in a series of 21 patients

C. Tsioutis · E. I. Kritsotakis · S. Maraki · A. Gikas

Received: 26 July 2009 / Accepted: 5 December 2009 / Published online: 9 January 2010
© Springer-Verlag 2009

Abstract Clinical reports on infections by pandrug-resistant (PDR) bacteria are scarce. This observational case series study was conducted during a 2-year period at a university hospital. Patients infected by PDR gram-negative bacteria comprised the study cohort. An isolate was defined as PDR if it was resistant to all antibiotic classes available for empirical treatment. A total of 21 patients infected by PDR gram-negative bacteria were recorded. The mean APACHE II score on admission was 18.8, the mean containing regimen (47.6%) or tigecycline (33.3%). All patients treated with tigecycline had total resolution of the infection and a notably shorter length of hospital stay after infection. In conclusion, PDR gram-negative bacterial infections are associated with considerable prolongation of hospitalization and mortality, although the mortality is not as high as that expected. Tigecycline appears to be effective for the successful treatment of PDR infections.

International Journal of Antimicrobial Agents 32 (2008) 450–454

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Short communication

Pandrug-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections: Characteristics and outcome in a series of 28 patients

Matthew E. Falagas[a,b,c,*], Petros I. Rafailidis[a,b], Dimitrios K. Matthaiou[a], Simona Virtzili[d], Dimitra Nikita[e], Argyris Michalopoulos[d]

ABSTRACT

We describe the characteristics and outcome of pandrug-resistant (PDR) Gram-negative bacterial infections (23 *Klebsiella pneumoniae* isolates, 3 *Pseudomonas aeruginosa* and 3 *Acinetobacter baumannii*) of hospitalised patients at a tertiary-care centre (1 January 2006–31 May 2007). The site of infection was central venous catheter-related in 5 of 24 patients with clinical infection, bacteraemia in 5, the respiratory system in 5, surgical site in 5, the urinary system in 2, the ascitic fluid in 1 and the central nervous system in one. Twenty of 24 patients with infection received an antibiotic regimen containing colistin (in combination with meropenem in 8 patients). The overall in-hospital mortality was 41.7% (10/24); 8 patients died because of the PDR infection (infection-related mortality 33.3%). Significant co-morbidity was present not only in the patients who died but also in survivors. PDR Gram-negative bacterial infections are associated with considerable mortality, although not as high as expected given the fact that the isolates were resistant to all tested antibiotics, including polymyxins. Antibiotics that are ineffective in vitro may prove life-saving for some of these patients, especially combination regimens containing colistin.

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SONUÇ

- Elimizdeki seçenekleri son derece dikkatle kullanmalıyız ! (AYP !!!)
- Direnç mekanizmalarını ve direnç kinetiğini daha iyi anlamalıyız !
- Standart, kolay ve kliniği en iyi yansıtan laboratuvar testleri geliştirmeliyiz.

SONUÇ

- İyi hastane hastane infeksiyonlarını önlemek için en çok uğraşan hastanedir
- İyi sağlık sistemi önleyici yaklaşımları en öncelikli olarak gören, önlemek için yapılanlara katkı sağlayan sistemdir.
- İnfeksiyon Hastalıkları Uzmanları ve diğer branşların “Tedavi” yerine “Önleyici” bir bakış açısına yoğunlaşmalarına ihtiyaç vardır.