Dirençli Gram Negatif Bakteriyel Enfeksiyonlar ve Tedavi Seçenekleri

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Dirençli Gram Negatif Bakteriyel Enfeksiyonlar

- Hastane enfeksiyonların tedavisinde ciddi problem
  - Mortalite, morbidite
  - Maliyet
  - Tedavi alternatiflerinin kısıtlı olması

Antibiyotikten kaçanlar!

***E** nterococcus faecium*	***E** nterococcus faecium*
***S** taphylococcus aureus*	***S** taphylococcus aureus*
***K** lebsiella pneumoniae*	***C** lostridium difficile*
***A** cinetobacter baumannii*	***A** cinetobacter baumannii*
***P** seudomonas aeruginosa*	***P** seudomonas aeruginosa*
***E** nterobacter spp*	***E** nterobacteriaceae*

Boucher HW et al.
Clin Infect Dis 2009;48:1-12.

Peterson LR.
Clin Infect Dis 2009;49:992

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.

Many different definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria are being used in the medical literature to characterize the different patterns of resistance found in healthcare-associated, antimicrobial-resistant bacteria. A group of international experts came together through a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international ter-

Uluslararası eksperler→ ECDC, CDC
CLSI, EUCAST, FDA sınır değerleri
Staphylococcus aureus, Enterococcus spp., Enterobacteriaceae* (Salmonella ve Shigella dışında), *Pseudomonas aeruginosa ve Acinetobacter spp

the United States Food and Drug Administration (FDA). MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. To ensure correct application of these definitions, bacterial isolates should be tested against all or nearly all of the antimicrobial agents within the antimicrobial categories and selective reporting and suppression of results should be avoided.

Clin Microbiol Infect 2012; **18:** 268–281

Tanımları kullanabilmek için kategorideki tüm ilaçların test edilmesi gerekir

P.aeruginosa

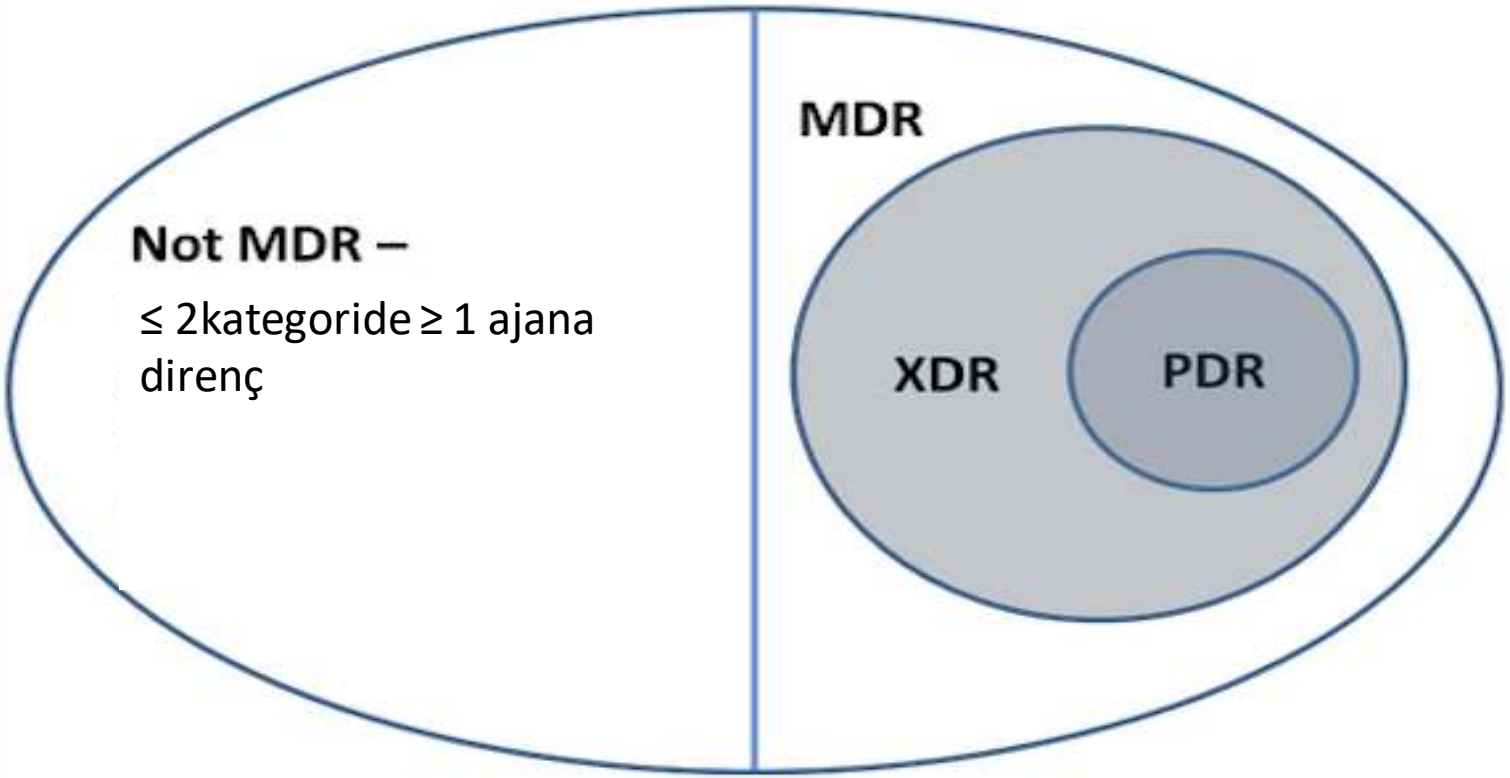
Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Antipseudomonal carbapenems	Imipenem
	Meropenem
	Doripenem
Antipseudomonal cephalosporins	Ceftazidime
	Cefepime
Antipseudomonal fluoroquinolones	Ciprofloxacin
	Levofloxacin
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid
	Piperacillin-tazobactam
Monobactams	Aztreonam
Phosphonic acids	Fosfomycin
Polymyxins	Colistin
	Polymyxin B

A.baumannii

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Antipseudomonal carbapenems	Imipenem
	Meropenem
	Doripenem
Antipseudomonal fluoroquinolones	Ciprofloxacin
	Levofloxacin
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam
	Ticarcillin-clavulanic acid
Extended-spectrum cephalosporins	Cefotaxime
	Ceftriaxone
	Ceftazidime
	Cefepime
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam
Polymyxins	Colistin
	Polymyxin B
Tetracyclines	Tetracycline
	Doxycycline
	Minocycline

Enterobactericeacea

Antimicrobial category	Antimicrobial agent
Aminoglycosides	Gentamicin
	Tobramycin
	Amikacin
	Netilmicin
Anti-MRSA cephalosporins	Ceftaroline (approved only for *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*)
Antipseudomonal penicillins + β-lactamase inhibitors	Ticarcillin-clavulanic acid
	Piperacillin-tazobactam
Carbapenems	Ertapenem
	Imipenem
	Meropenem
	Doripenem
Non-extended spectrum cephalosporins: 1st and 2nd generation cephalosporins	Cefazolin
	Cefuroxime
Extended-spectrum cephalosporins: 3rd and 4th generation cephalosporins	Cefotaxime or ceftriaxone
	Ceftazidime
	Cefepime
Cephamycins	Cefoxitin
	Cefotetan
Fluoroquinolones	Ciprofloxacin
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
Glycylcyclines	Tigecycline
Monobactams	Aztreonam
Penicillins	Ampicillin
Penicillins + β-lactamase inhibitors	Amoxicillin-clavulanic acid
	Ampicillin-sulbactam
Phenicols	Chloramphenicol
Phosphonic acids	Fosfomycin
Polymyxins	Colistin



MDR (multi-drug resistant)

≥ 3 kategorideki ilaçlardan en az birine direnç

XDR (extensively drug resistant

≤ 2'si hariç (1 veya 2 duyarlı) tüm kategorilerdeki ilaçlardan en az birine direnç

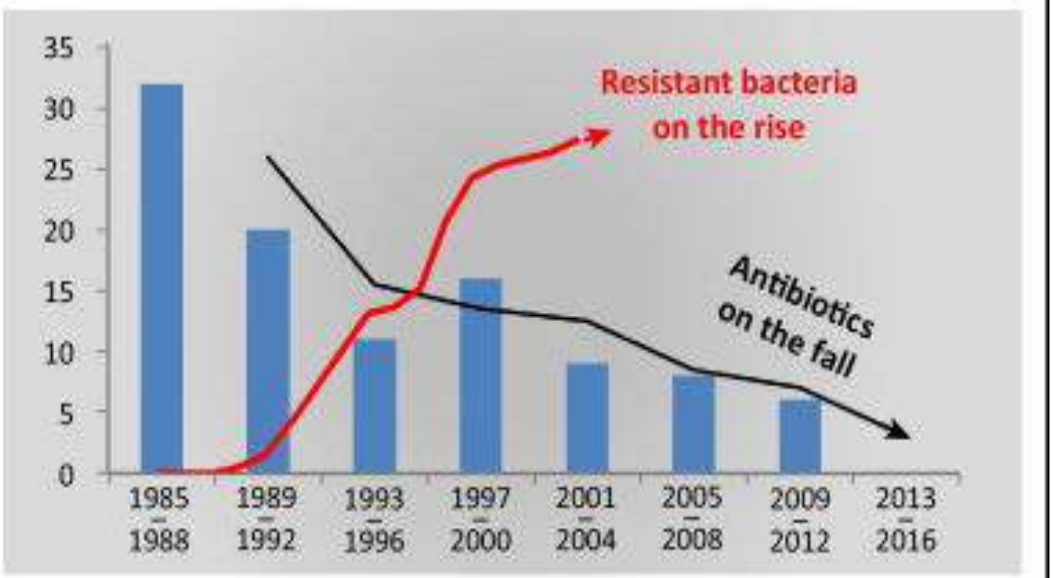
PDR (pan-drug resistant)

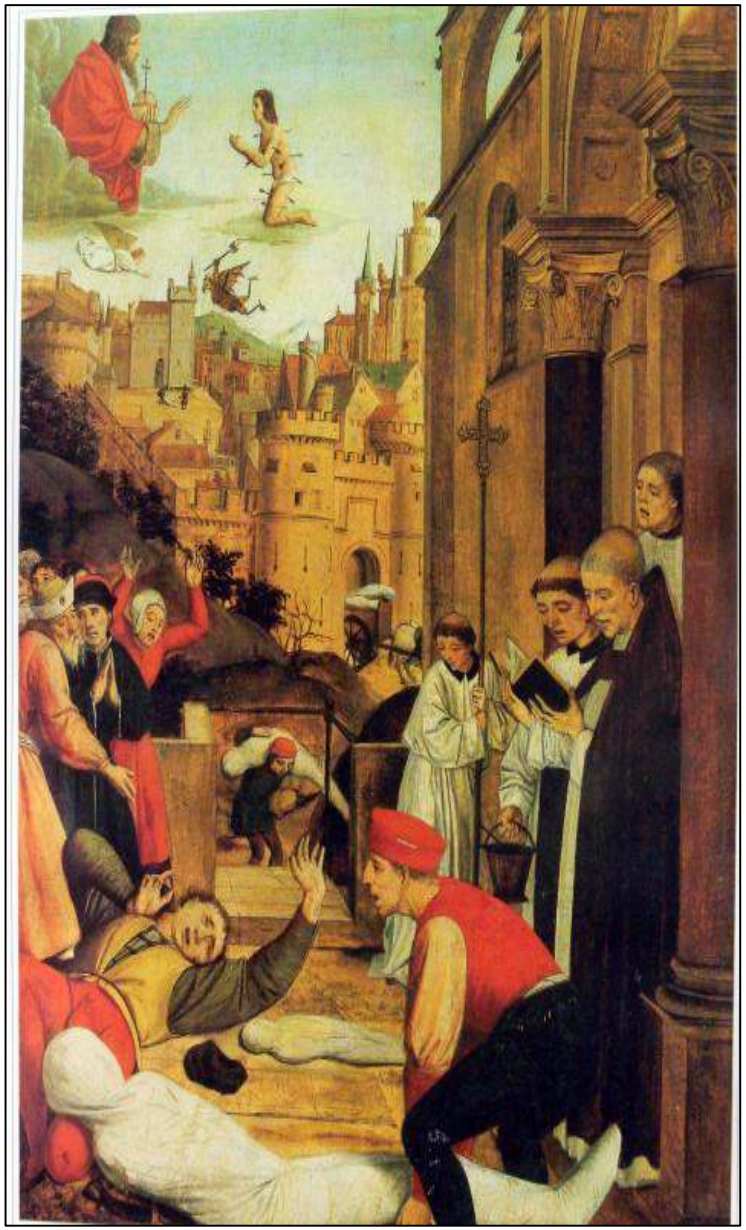
Tüm antibiyotik kategorilerindeki ilaçlara direnç

New antimicrobials in development with gram-negative activity

Product	Antimicrobial Class	Trial Status
ceftolozane/tazobactam	cephalosporin/beta-lactamase inhibitor combination	Phase 3
ceftazidime/avibactam	cephalosporin/beta-lactamase inhibitor combination	Phase 3
ceftaroline/avibactam	cephalosporin/ beta-lactamase inhibitor combination	Phase 2
imipenem/MK-7655	carbapenem/ beta-lactamase inhibitor combination	Phase 2
plazomicin	aminoglycoside	Phase 2
eravacycline	fluorocycline	Phase 2
brilacidin	peptide defense protein mimetic	Phase 2

Source: Brock J





Yoğun antibiyotik kullanımı

Çoklu dirençli patojen

Ek veya farklı geniş spektrumlu antibiyotikler

Yeni direnç gelişimi

Şiddetli enfeksiyonlar

Tedaviye başlarken

- Sepsis, VİP gibi şiddetli enfeksiyonlarda özellikle dirençli GNB enfeksiyon düşünülüyorsa, 2 antimikrobiyal ajanla daha geniş bir antimikrobiyal kapsama
- İdentifikasyon, duyarlılık sonuçları
- Kombinasyon tedavisi
  - Derin nötropenik
  - *P. aeruginosa* sepsisi
  - YBÜ hastaları
  - VİP hastaları için düşünüldü

Tamma P, etal, 2012, Clin. Microbiol Rev.

Tedaviye başlarken

- Çoklu direncin geliştiği bu dönemde potansiyel patojenleri kapsayan empirik antibiyotik tedavisi gündeme geldi
- Mortalite;
  - Etkin olmayan bir antibiyotiğin alınması
  - Geç başlanması

Tedaviye başlarken

- Empirik antibiyotiğin seçilmesi için lokal epidemiyoloji bilinmeli
- Gram negatiflerde direncin artması ciddi enfeksiyonlarda empirik tedavinin seçilmesini zorlaştırıyor

ESBL (+) patojenlerle enfeksiyonlarda ESBL (-) olanlara göre uygun tedaviyi alma süresi daha uzun (ort. 72 sa, ort. 11.5 sa)

Lautenbach E, Clin. Infect Dis. 2001

Tedaviye başlarken

- Hastanın özelliğine göre empirik tedaviyi bireyselleştirmek
  - Kolonizasyonu
  - Önceki antibiyotik kullanımı
  - Hastanede yatışı
  - Kateter varlığı
- Önceden kolonizasyonunun bilinmesi ve aldığı tedavilerin bilinmesi empirik tedavinin yeterliliğini arttırır

  Bhat S. et al. Int Journal Antimicrobiol Agents. 2007

- Deeskalasyon önemli

Kombinasyon tedavisi

Amaç

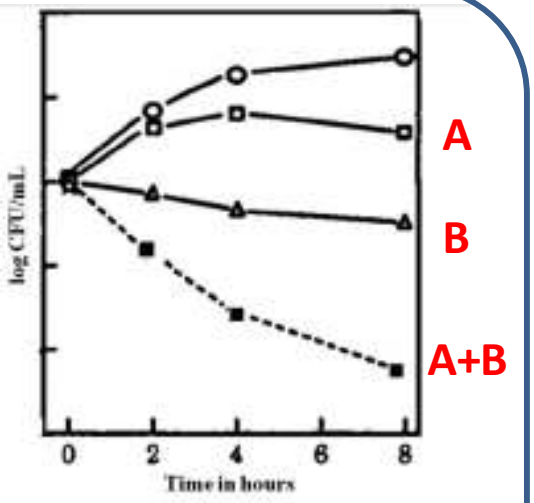
- Spektrumu genişletmek
- Sinerji
- Antibiyotik tedavisi sırasında direnci önlemek veya geciktirmek

Risk

- Yan etki (nefrotoksisite vs.)
- Maliyet
- CDI, fungal enfeksiyonlar
- Direnç , ilaç etkileşimleri

Sinerji

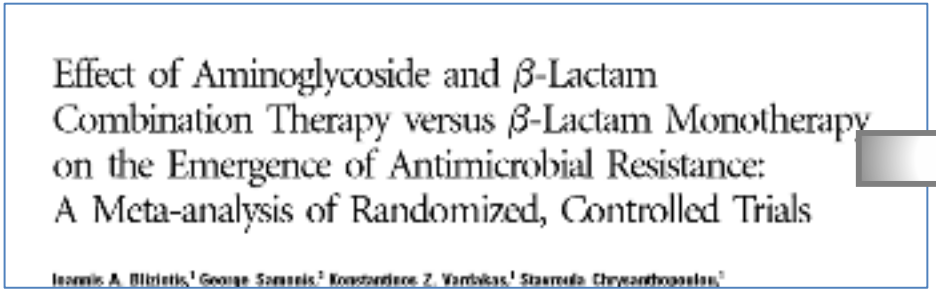
- Kombinasyonun bir diğer avantajı
- Daha hızlı patojen öldürme
- *P.aeruginosa*
  - Beta-laktam- AG ve imipenem- sipro.
- Gram negatif patojenler
  - Seftazidim+ sipro ve PIP/TZB +sipro.
- Mevcut verilere göre AG- sipro. sinerjisi yok



Bakterisidal aktivitede monoterapiye göre **> 2 log artış** olması

Direncin önlenmesi

- *M. tuberculosis*'den yola çıkılmış (daha yavaş ürer, yavaş gelişen bir direnç)
- Kistik fibroz'da
  - MİK değerlerinde anlamlı değişim
- Klinik veriler, küçük seriler


Effect of Aminoglycoside and β-Lactam Combination Therapy versus β-Lactam Monotherapy on the Emergence of Antimicrobial Resistance: A Meta-analysis of Randomized, Controlled Trials

Ioannis A. Bliziotis,[1] George Samonis,[2] Konstantinos Z. Vardakas,[1] Stavroula Chrysanthopoulou,[1]

Geniş spektrumlu beta laktamlar monoterapide dirence yol açmıyor

Clinical Infectious Diseases 2005;41:149–58

Tedavi stratejileri/seçenekleri

- Yapılan çalışmalar
  - İnvitro duyarlılık ve sinerji çalışmaları
  - İnvivo modellerde etkinlik çalışmaları
  - Retrospektif klinik çalışmalar (tek merkezli)
    - Kombinasyon-monoterapi karşılaştırmalı
    - Farklı kombinasyonlar karşılaştırmalı
  - Prospektif RKÇ (sayıca az)
  - Olgu serileri
  - Metaanalizler

Çoklu dirençli gram negatiflerde monoterapi ve kombinasyon tedavisini karşılaştıran çalışmalar

Reference	Design (*n*)	Infection	Drug combination	combination therapy)	Conclusion(s)
52	Prospective, randomized (53)	*Pseudomonas aeruginosa* cystic fibrosis exacerbations	Colisin (2 million IU q8h) vs colistin plus aztreonam, piperacillin, ceftazidime, imipenem, or ciprofloxacin	100% vs 100% (clinical response at day 12); significant decrease in creatinine clearance in combination therapy group (nephrotoxicity)	No difference in response rates; nephrotoxicity increased with combination therapy
55a	Prospective, observational (162)	Metallo-β-lactamase-producing *Klebsiella pneumoniae* bacteremia	Single active agent vs carbapenem plus either colistin or aminoglycoside	27% vs 8.3% (mortality)	Patients treated with a carbapenem plus either colistin or an aminoglycoside tended to have higher survival that
74	Retrospective (71)	MDRGN infections (multiple sites)	Colistin vs colistin plus meropenem		
73	Retrospective (258)	MDRGN infections (multiple sites)	Colistin vs colistin plus meropenem, ampicillin-sulbactam, or piperacillin-tazobactam		
103	Retrospective (33)	Carbapenem-resistant *Acinetobacter baumannii*	Tigecycline vs tigecycline plus aminoglycoside		
150	Prospective, observational (16)	Carbapenem-resistant *K. pneumoniae* bacteremia	Polymyxin B vs polymyxin plus tigecycline		resistance to these agents
154	Prospective, observational (23)	MDR *P. aeruginosa* (multiple sites)	Colistin (1-5 mg/kg/day) vs colistin plus amikacin or antipseudomonal β-lactam	60% vs 62% (clinical response)	No difference in response rates
243	Retrospective (8)	MDR *P. aeruginosa* diabetic foot infections	Colistin (1 million IU q12h) vs colistin plus rif or imipenem	75% vs 50% (response rates);	No difference in response and

Kolistin +
- Aztreonam
- Piperasilin
- Seftazidim
- İmipenem
- Siprofloksasin
- Aminoglikozidler
- Ampisilin sulbaktam
- Tigesiklin
- Rifampin

Tamma P, et al, 2012, Clin. Microbiol Rev.

Çoklu dirençli gram negatiflerin tedavisi

- Bu rejimler artık kurtarma tedavileri gibi düşünülüyor
- Bu rejimlere de direnç gelimesi riski göz önünde bulundurularak kombine tedavi kullanılmalı
- Uzamış antibiyotik infüzyon stratejileri de beta laktamların MİK değerleri üzerinde olması gereken patojenlere karşı kullanılabilir

Tedavi seçenekleri

- Eğer patojen MDR ise ve karbapenemaz üretiyorsa
  - %98 kinolonlara dirençli
  - %50 AG'lere dirençli

Bratu S et al, J Antimicrob Chemother. 2005

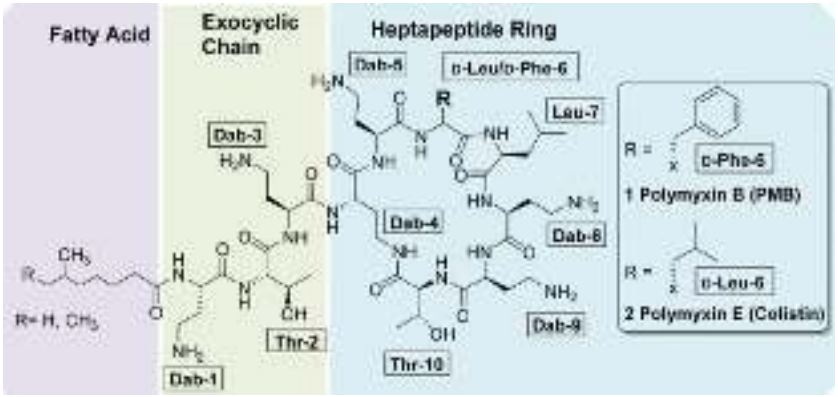
- Geriye
  - Polimiksinler
  - Tigesiklin
  - Fosfomisin
  - Diğer

Kolistin

- Polimiksinler (A→E)
- Kolistin: polimiksin E
  - Kolistin sülfat
  - Kolistin metanesülfat (parenteral)
- Etkinlik
  - *Enterobactericeacea* (karbapenemaz üreten dahil)
  - *H.influenzae, L.pneumophilia*
  - Dirençli *P.aeruginosa, Acinetobacter spp.*
  - *S. maltophilia*
  - *…*

Kolistin

- Siklik peptid, uzun hidrofobik kuyruk



- Fosfolidlerle etkileşerek bakteri hücre membranını bozar
- LPS'lere toksik (gram negatiflerde)
- Anti-endoksin etki (LPS'yi bağlar, nötralize eder)
- Bakterisidal

Kolistin monoterapisi

- Kolistin heteroresistansı özellikle MDR-AB'de subgrupların direncinde invitro gösterilmiş
- Önerilen kolistin dozları ile sağlanan 0.5-3.5 mg/L plazma konsantrasyonu bu dirençli subgrupları eradike etmede yeterli değil
- Daha önce kolistin kullananlarda heteroresistans daha fazla
- Kolistin difüzyonunun düşük olduğu organlarda direnç gelişme riski daha fazla (pulmoner parankim, plevral kavite)

- Bu nedenlerle monoterapi önerilmiyor

Kolistin monoterapisi

- Farklı görüşlerde var…

Kasiakov et al. 2005: karbapenem dirençli gram negatif bakterilerde kolistin monoterapisi, kolistin+ meropenem ile karşılaştırıldığında MONOTERAPİ daha başarılı

Neonakis et al. 2011: MDR-AB'e bağlı VİP
Kolistin monoterapisi, kolistin+ rifampisin kadar etkili bulunmuştur

Crit Care Med. 2015 June ; 43(6): 1332–1334.

Combination Therapy for Extreme Drug Resistant (XDR) *Acinetobacter baumannii*: Ready for Prime-Time?

Brad Spellberg, MD[1] and **Robert A. Bonomo, MD**[2,3,4]

- YBÜ'lerinde karbapeneme dirençli (ABD)
  - *A.baumannii* izolatlarının %50'si
  - *P.aeruginosa* %20'si
  - *K.pneumonia* % 10'u
- XDR *A.baumannii*'de VİP ve bakteremi mortalitesi ≥ %50
- Karbapenem direnci mortaliteyi 3-4 kat arttırıyor
- Etkin olmayan empirik tedavi mortaliteyi arttırıyor

Yeni antibiyotikler

- **Seftalozan-tazobaktam** (*Acinetobacter spp.* üzerine belirgin etkinliği yok)
- **Seftazidim-avibaktam**'ında etkinliği seftazidim gibi
- **Eravacyclin** invivo etkinliği tigesiklin gibi

Şu anki tedavilere üstün olduğu gösterilmiş yeni antibiyotikler yok
Sonuçları daha iyi hale getirmek için "kombinasyon tedavileri" öne sürülüyor

Spellberg B, Crit Care Med. 2015

Kombinasyonlar- *A. baumannii*

Kolistin+rifampisin

- En çok test edilenlerden
- Küçük çaplı çalışmalar var
- Deneysel modeller
- Durante et al, (2013) Çalışması
  - Multisenter ,randomize

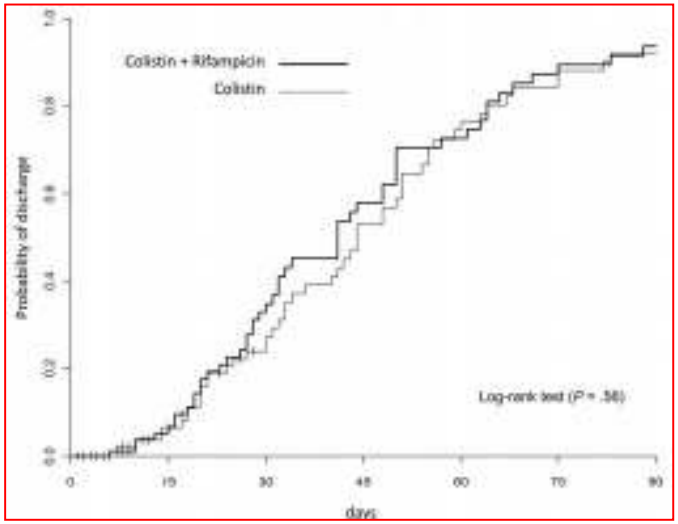
Spellberg B, Crit Care Med. 2015

Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

Clin Infect Dis. 2013;57(3):349-58

Emanuele Durante-Mangoni,[1] Giuseppe Signoriello,[2] Roberto Andini,[1] Annunziata Mattei,[3] Maria De Cristoforo,[4] Patrizia Murino,[5] Matteo Bassetti,[5,a] Paolo Malacarne,[6] Nicola Petrosillo,[7] Nicola Galdieri,[3] Paola Mocavero,[3] Antonio Corcione,[3] Claudio Viscoli,[5] Raffaele Zarrilli,[8] Ciro Gallo,[2] and Riccardo Utili[1]

→Çok merkezli
→Açık etiketli



→30 günlük mortalite
→Hastanede yatış süresi
"fark yok"

Kombinasyon ile mikrobiyolojik eradikasyon başarılı (p=0.034)

PLOS ONE

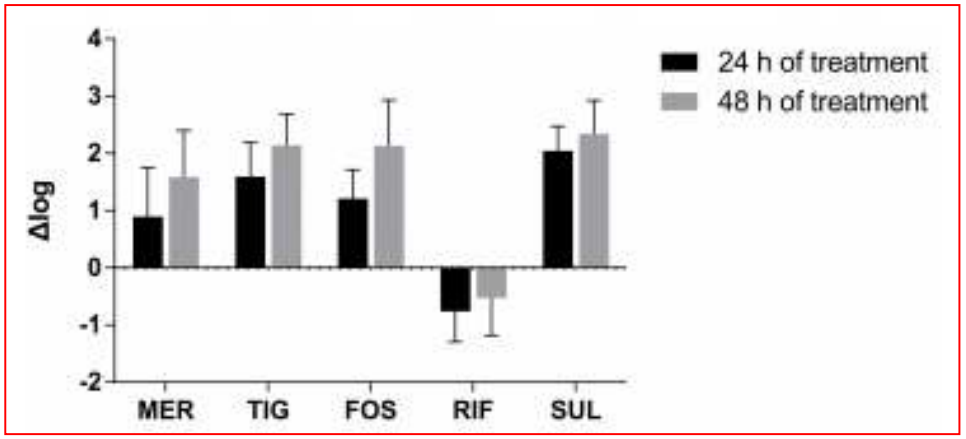
Bing Fan et al. PLoS One. 2016; 11(6)

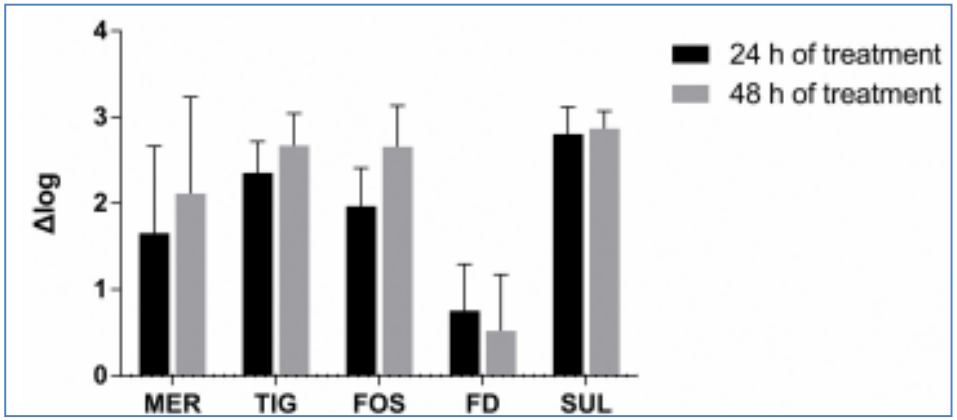
RESEARCH ARTICLE

Activity of Colistin in Combination with Meropenem, Tigecycline, Fosfomycin, Fusidic Acid, Rifampin or Sulbactam against Extensively Drug-Resistant *Acinetobacter baumannii* in a Murine Thigh-Infection Model

- Kolistin + meropenem
  + tigesiklin
  + fosfomisin
  + fusidik asit
  + sulbaktam
  + rifampisin

Yüksek MİK konsantrasyonunda monoterapiye üstün değil





- XDR *A.baumannii* tedavisinde **fusidik asit ve rifampisin** kombinasyonları daha etkili

- Meropenem ile kombinasyon **MİK ≤ 32** ise alternatif olabilir

Rifampisin

- Rifampisinin kombinasyon tedavisinde uygulandığı iki dirençli gram negatif
  - *A.baumannii*
  - *P.aeruginosa*

  Sinerjizm invitro ve invivo çalışmalarda
- Hidrofobik, gram negatif duvarından geçemez
- Kolistin dış membranı geçirgen hale getirir
- Kolistin ile daha az toksik kombinasyon (hepatik/renal)

Rifampisin

- Yüksek MİK değerleri daha az duyarlı yapmaz, penetrasyonu azalır
- Kolistin ve karbapenemle olan etkinliği rifampisine olan dirençten etkilenmez
- MDR, karbapenemaz üreten AB'e karşı rifampisin;
  - İmipenem, sulbaktam/ampisilin, kolistin ile sinerjik
  - Rifampisin MİK yüksek olsa bile sinerjik

Tripodi et al, Int J Antimicrob Agents. 2007

Yapılan çalışmalar yeterli değil, klinik açıdan değerlendiren kontrollü çalışmalar gerek

- Büyük moleküllü antibiyotiklerin girişi kolistinin XDR-AB'nin dış membranını parçalaması ile kolaylaşır

  - Kolistin/daptomisin ile invitro sinerji

  (Yang H, et al. Int J Antimicrob Agents. 2015; 45:188–191.)

  - Kolistin/glikopeptid ile invitro sinerji

  (Hornsey M, et al. Antimicrob Agents Chemother. 2011; 55:3534–3537)

- İnvitro sinerjiye rağmen invivo modellerde başarılı değil!!

  - Kolistin/tigesiklin ile XDR-AB'e karşı akciğer dokusunda anlamlı etkinlik yok

  (Mutlu Yilmaz E, et al. Int J Antimicrob Agents. 2012; 40:332–336.)

  - Sulbaktam/kolistin, sulbaktam/tigesiklin CR-AB sepsisi

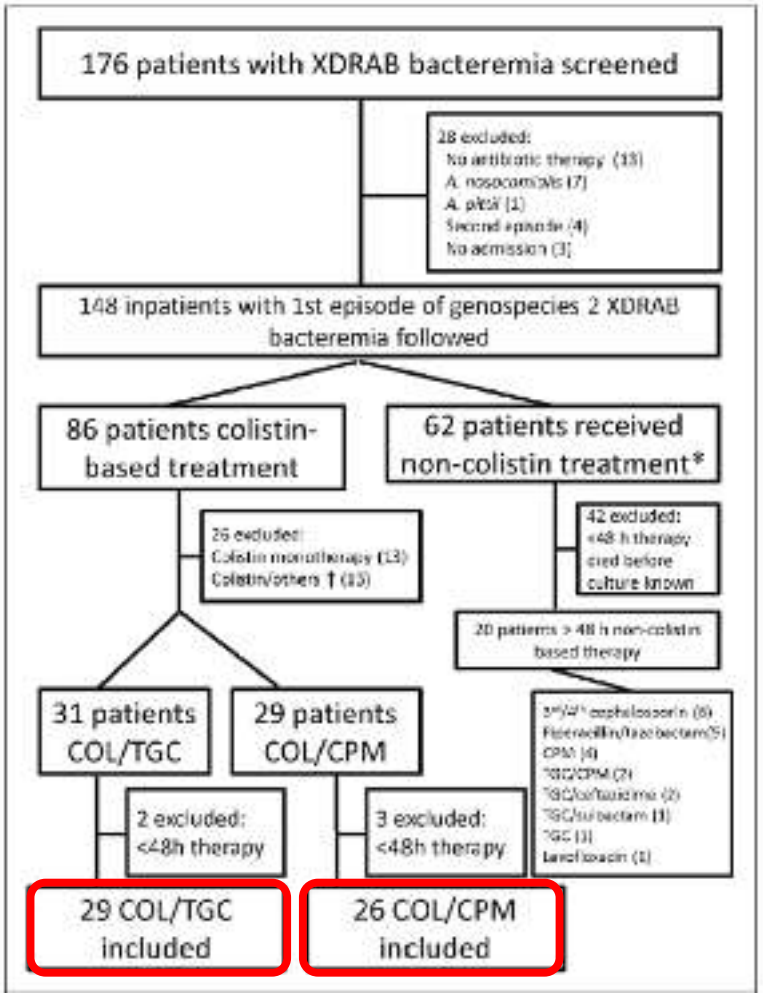
  (Dinc G, et al. Chemotherapy. 2013; 59:325–329.)

Kombinasyonlar- *A. baumannii*

- Kolistin+tigesiklin
- Kolistin+karbapenem (dirençli olsa bile invitro sinerji)

Excess Mortality Associated With Colistin-Tigecycline Compared With Colistin-Carbapenem Combination Therapy for Extensively Drug-Resistant *Acinetobacter baumannii* Bacteremia: A Multicenter Prospective Observational Study

- Retrospektif, sayı az
- 14-gün mortalitesi
  - COL/CPM %15
  - COL/TGC %35
- Bakteriyemi nüks TGC'de fazla
- TGC MİK değeri ≥ 2 ise mortalite x7 kat fazla
- TGC MİK <2 ise sonuçlar benzer



Cheng A et al. Crit Care Med. 2015. 43(6):1194-204.

Chuang et al. BMC Infectious Diseases 2014, 14:102
http://www.biomedcentral.com/1471-2334/14/102

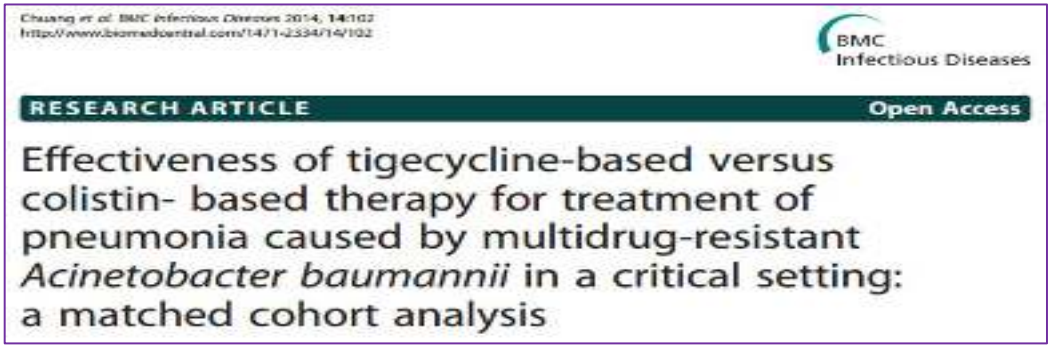
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Effectiveness of tigecycline-based versus colistin- based therapy for treatment of pneumonia caused by multidrug-resistant *Acinetobacter baumannii* in a critical setting: a matched cohort analysis

- Diğer çalışma ile uyumlu
- 294 hasta (COL vs TGC)
- **Tigesiklin MİK≥2 µg/ml, mortalite ile ilişkili**

- Akciğer ve kanda *A.baumannii* için direnci gösteren MİK değeri diyebiliriz
- İster kombinasyon tedavisi olsun ister monoterapi bu suşlarla olan **bakteriyemi ve pnömonide tigesiklin daha yüksek mortalite ile ilişkili**



Excess Mortality Associated With Colistin-Tigecycline Compared With Colistin-Carbapenem Combination Therapy for Extensively Drug-Resistant *Acinetobacter baumannii* Bacteremia: A Multicenter Prospective Observational Study

- Bu iki çalışma hangi kombinasyon uygulanmamalı!!!

Tigesiklin

- Parenteral minosiklin analogu
- Polimikrobiyal enfeksiyonlarda monoterapi (MDR patojenler dahil)
- Gram negatif spektrumu: MDR *A.baumanni*, ESBL Enterobacter, KPC ve VIM üreten *K.pneumoniae, S.maltophilia*
- *Yükleme dozu 100mg, 50mg 2x1 (1 saat infüzyon)*

Tigesiklin

- Yarı ömrü 37 ± 12 saat
- Safra, safra kesesi kolonda kinetiği oldukça iyi
- Akciğer dokusu halen tartışmalı
- GİS yan etkileri (bulantı,kusma, diyare, anoreksi)
- MDR epidemiyolojisi olan (öz. KPC fazla ise) aminoglikozid ve kolistinin, tigesiklin ile kombinasyonu etkili olabilir

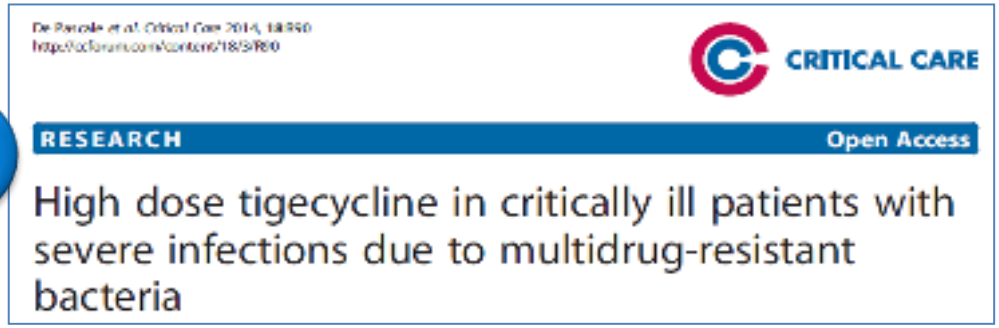
- Tigesiklinin kan düzeyinin düşük olması direnci tetikliyor olabilir

Hedeflenen patojen için MİK değeri, Cmax'ı aşıyorsa (AB türlerinde!!) direnç gelişimi ortaya çıkabilir

Peleg AY, J Antimicrob Chemother.2007

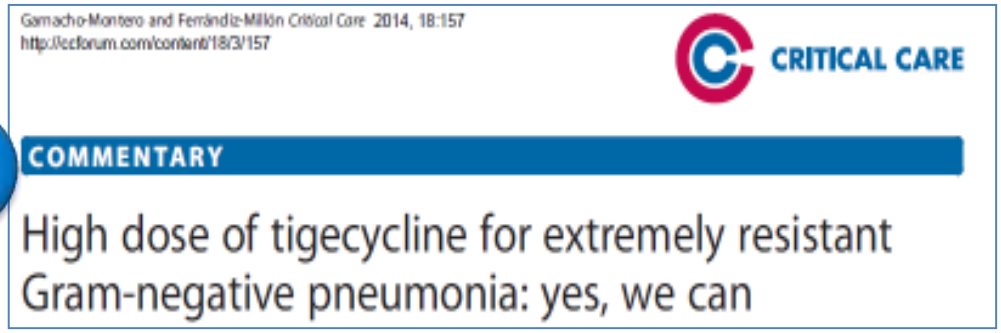
Yüksek doz tigesiklin

1



- CRAB ve CRKP
- 200mg (yükleme), 100mg (12 sa'de bir)
- Normal doz yeterli değil
- Direnci tetikler
- Toksisite yok

2



- Karşılaştırmalı klinik çalışma
- VİP'te yüksek doz etkin
- Sınırlamaları var
  - Ekte kullanılan antibiyotikler
  - Retrospektif
  - Az sayıda hasta

3

%25 hasta sürekli renal replasman alıyor
Her iki grupta dağılımı ???
Tigesiklin lipofilik
Proteine ↑bağlanır, hemodiyalizle atılır
Bu hastalarda yüksek doz önerilebilir

Yüksek doz tigesiklin-Karşılaştırmalı çalışmalar

First author, year	Study design, period; country	No. of patients receiving TIG; site of infection and causative pathogen	i.v. TIG dosing regimen	Rationale for using high-dose TIG	Concomitant antibiotic treatment	Effectiveness (high-dose vs. low-dose)		Adverse events (high-dose vs. low-dose)
						Mortality	Clinical cure	
Comparative studies (high-dose versus low-dose)								
De Pascale (2013) [20]	SC, retrospective cohort (poster), 2009–2011; Italy	100 ICU patients; severe infections due to *Acinetobacter baumannii* and *Klebsiella pneumoniae*	100 mg q12 h vs. 50 mg q12 h	To evaluate potential benefits of higher doses of TIG	NR[a]	NR[b]	VAP subpopulation, 19/33 (57.6%) vs. 10/30 (33.3%); $P = 0.08$	NR[c]
Di Carlo (2013) [21]	SC, prospective case series, 2001–2012; Italy	30 ICU patients with severe IAIs due to XDR KPC-3 *K. pneumoniae* ST258 clone	200 mg LD + 100 mg q12 h vs. 100 mg LD + 50 mg q12 h	To treat severe intra-abdominal abscesses	i.v. colistin 5 mg/kg in three equal daily doses	1/12 (8.3%) vs. 11/18 (61.1%); $P = 0.005$[d]	NR	No adverse events
Ramirez (2013) [16]	MC, phase 2, DB RCT, 2008–2011; Europe, Asia, America, Australia	71 patients/episodes with nosocomial pneumonia[e]	200 mg LD + 100 mg q12 h vs. 150 mg LD + 75 mg q12 h	Lower cure rates with standard-dose TIG than imipenem/cilastatin in a previous study on patients with HAP	i.v. ceftazidime 2 g q8 h + i.v. tobramycin 7 mg/kg or amikacin 20 mg/kg + i.v. vancomycin placebo[f]	3/35 (8.6%) vs. 7/36 (19.4%); P = NS	At TOC, 17/20 (85.0%) vs. 16/23 (69.6%); P = NS	Diarrhoea 14.3% vs. 2.8%; nausea 8.6% vs. 2.8%; vomiting 5.7% vs. 2.8%; (P = NS for all comparisons)
Balandin Moreno (2011) [17]	SC, prospective cohort (poster), 2009–2010; Spain	44 episodes (37 ICU patients) due to Enterobacteriaceae or non-fermentative Gram-negative bacilli[g]	100 mg q12 h vs. 50 mg q12 h[h]	To analyse their experience with high-dose TIG in ICU patients	Carbapenems (16), colistin (12), β-lactams (10), quinolones (5), other (4)	7/27 (26%) vs. 1/13 (8%); P = NS	NR	NR
Single-arm studies (only high-dose)								
Sbrana (2013) [23]	SC, retrospective cohort, 2011–2012; Italy	26 episodes (22 patients) trauma ICU patients; KPC *K. pneumoniae* infections[i]	100 mg q12 h	NR	i.v. gentamicin, i.v. colistin, i.v. fosfomycin[j]	All-cause, 3/26 (11.5%); infection-related, 2/26 (7.7%)	24/26 (92.3%)	No adverse events in 25 episodes where TIG was administered
Humphries (2010) [22]	Case report, NR; USA	49-year-old male; bacteraemia due to K *pneumoniae*			in (i.v. and d), cin	Survived	Cured	NR
Dandache (2009) [19]	Case report, NR; USA	42-year-old male; meningitis due to XDR *K. pne*	100 mg q12 h	Due to severity of illness and	No	Survived	Cured	NR
Cunha (2007) [18]	Case report, NR; USA	Elderly male; UTI MDR *K. pneumoni* *Enterobacter aerogenes*		*pneumoniae* with high-dose TIG		Survived	Cured	NR

8 çalışma, 263 hasta, %58 kritik

Şiddetli enfeksiyonlarda yüksek doz

International Journal of Infectious Diseases 33 (2015) 132–134

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

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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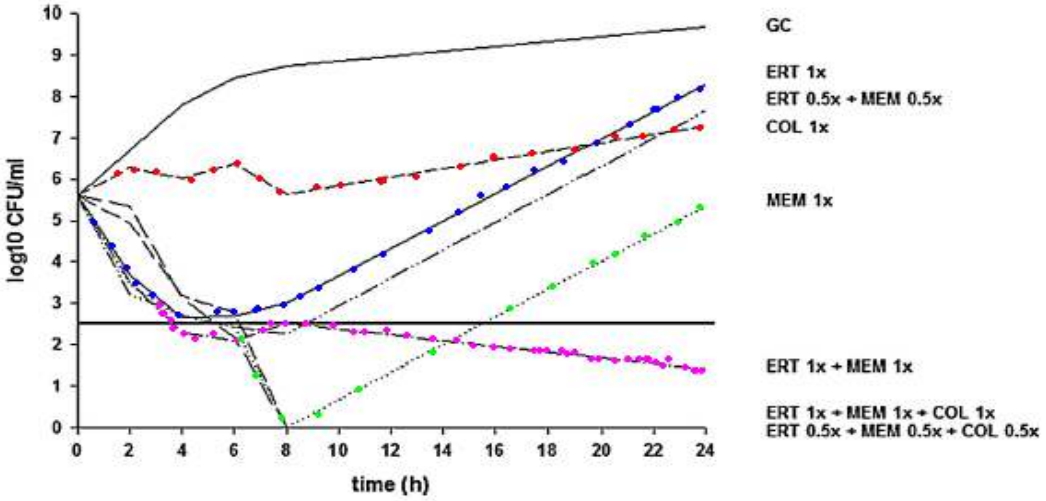
İkili karbapenem kullanımı

- Bakteriyemi , PDR KP
- MİK değerleri
  - ERT:128 µg/ml
  - MEM: 256 µg/ml
  - COL: 32 µg/ml
- **7. günde kolistin kesilmiş,** ERT ve MEM 14 güne tamamlanmış

Zaman öldürme (time kill) eğrisi



Yüksek MİK değerlerinde bile sinerjik etki

İkili karbapenem kullanımı

- İnvitro çalışmalarda sinerjik etki
  - Yüksek MİK değerlerinde bile

  (*Oliva A et al, J. Antimicrobial. Chemoter 2014*)
- Kolistinin eklenmesi hücre membranını parçalayıp diğer ilaçlar için yeterli intrasellüler konsantrasyonu sağlaması
- **Ertapenem intihar molekülü gibi-** karbapenemaza affinitesi var, enzimleri bağlar
- Diğer karbapenem bakterisidal etki gösterir

AAC Journals.ASM.org

CHALLENGING CLINICAL CASE IN ANTIMICROBIAL RESISTANCE

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Jose F. Camargo,[a] Jacques Simkins,[a] Thiago Beduschi,[b] Akin Tekin,[b] Laura Aragon,[c] Armando Pérez-Cardona,[d] Clara E. Prado,[e] Michele I. Morris,[a] Lilian M. Abbo[a]

Rafael Cantón (Commentator)[f,g]

Department of Medicine, Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, Florida, USA[a]; Miami Transplant Institute and Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA[b]; Department of Pharmacy, Jackson Memorial Hospital, Miami, Florida, USA[c]; Department of Microbiology, Jackson Memorial Hospital, Miami, Florida, USA[d]; Department of Microbiology, University of Miami, Miami, Florida, USA[e]; Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain[f]; Red Española de Investigación en Patología Infecciosa (Madrid, Spain[g]

- KPC-KP, intraabdominal enfeksiyon
  - Tigesiklin
- BAL, CRKP (TGC:R, COL:S)
  - Kolistin+ uzamış infüzyon MER
- CRKP, bakteriyemi, kateter, idrar
  - Kolistin + uzamış infüzyon MER + TGC
  - Kolistin + uzamış infüzyon MER + ERT
- Breakthrough bakteriyemi [**COL:R (MİK=12)**, TGC:R]
  - CAZ-AVI + ERT (invitro sinerji)

(0.25g/1g iv/q8h)

Camargo CF, Antimicrob Agents Chemother. 2015 ;59(10):5903-8

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Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

- CR-KP bakteremisi, mortalitesi çok yüksek, >%50
  - Tigesiklin (…
  - Kolistin (…
- Kolistin ve tigesiklin de dirençli hale geliyor
- Avrupa'da intravenöz fosfomisin kullanılıyor
  - Etkin, yan etki nadir ama tedavi sırasında hızlı direnç
- CEF-AVI (sefatazidim-avibaktam)
  - Komplike İAE ve ÜSE, pnömoni (faz 3)

Seftazidim - Avibaktam

- Avibaktamın eklenmesi ile seftazidim *Enterobactericeacea* etkinliği x 4-1024 kat ↑ (seftazidime dirençli olsa bile)
- ESBL, KPC'ye etkili
- Metalo-betalaktamazlara (VIM,NDM, IMP) etkili değil
- İnvitro çalışma; 1466 GNB izolatı
  - Kan dolaşımı etkeni olanların %99.8'i
  - Pnömoni olanların %99.4'ü
  - İAE ve ÜSE olanların %100'ü

CAZ-AVİ
MİK ≤ 4µg/ml

↑

CLSI'ın sadece CAZ için duyarlı belirttiği değer

İkili karbapenem

Ertapenemin karbapenemaz affinitesi fazla olduğu için genellikle meropenem ve doripenem ile kombinasyonları
Bazen kolistin ikili kombinasyona ekleniyor

Reference or source and country	Underlying disease(s)	Clinical sample(s)	Microorganism	Drugs and MICs (μg/ml)[a]	Dual-carbapenem therapy (dose and infusion conditions when included)	Treatment duration, comments, and outcome
Giamarellou et al. (11), Greece	Spinal cord injury	Blood, urine, CVC	KPC-2-producing *K. pneumoniae*	ERT, >8; MER, >32; DOR, >8; CST, >16	ERT (1 g q24h i.v.) + DOR (2 g q8h i.v., 4-h infusion, 1 h after ERT)	20-day treatment. Patient became afebrile on day 4 with negative blood and cultures after 2 days of treatment. No relapse after 10 mos of follow-up.
	Subarachnoid hemorrhage	Blood, urine	KPC-2-producing *K. pneumoniae*	ERT, >8; MER, >32; DOR, >8; CST, >16	ERT (1 g q24h i.v.) + MER (1 g q8h i.v., 3-h infusion, 1 h after ERT)	14-day treatment. MER dose reduced due to renal function. Patient became afebrile on day 3, and blood and urine cultures were sterile during therapy and after 3-wk follow-up.
	Spinal cord injury	Urine	KPC-2-producing *K. pneumoniae*	ERT, >8; MER, >32; DOR, >8; CST, >16	ERT (1 g q24h i.v.) + MER (2 g q8h i.v., 3-h infusion, 1 h after ERT)	10-day treatment. Sterile urine cultures after 2 days of treatment. No relapse after 6 mos of follow-up
Ceccarelli et al. (12), Italy	Cerebral hemorrhage	Blood, endotracheal aspirate	KPC-3-producing *K. pneumoniae*	ERT, 256–512; MER, 64; DOR, 32–64; CST, 16–31	ERT (0.5–1 g q24h i.v.) + DOR (0.25–1 g q8h i.v., 4-h infusion)	21-day treatment. Bacteremia cleared after 8-day of treatment. ERT and DOR doses were adjusted during treatment to renal clearance. No relapse 1 mo after end of treatment.
Oliva et al. (25), Italy	Aortic prosthesis replacement	Blood	Carbapenemase-producing *K. pneumoniae*	ERT, 128; MER, 256; CST, ≥16	ERT (1 g q24h i.v.) + MER (2 g q8h i.v.)	21-day treatment. Recovered after treatment.
	Left lower limb revascularization	Blood	Carbapenemase-producing *K. pneumoniae*	ERT, 256; MER, 256; CST, ≥16	ERT (0.5 g q24h i.v.) + MER (1 g q12h i.v.)	MER adjusted to renal function. Microbiological eradication after 48 h of treatment. Death due to heart failure after 4 days of treatment.
	Renal hematoma	Blood	Carbapenemase-producing *K. pneumoniae*	ERT, 256; MER, 128; CST, ≥16	ERT (1 g q24h i.v.) + MER (2 g q8h i.v.)	24-day treatment. Clinical recovery.
	Hip joint replacement	Blood, CVC	Pan-drug-resistant *K. pneumoniae*	ERT, 128; MER, 256; CST, 32	ERT (1 g q24h i.v.) + MER (2 g q8h i.v., 4-h infusion) + CST (6 MU loading dose, 4.5 MU q12h)	21-day treatment (7 days with CST). Sterile blood and urine cultures after 4 days of treatment.
Chua et al. (27), Singapore	Necrotizing pancreatitis	Sputum	KPC-producing *K. pneumoniae*	ERT, 4; MER, 16; DOR, 8; POL-B, 1	ERT (1 g q24h i.v.) + DOR (1 g q8h i.v., 4-h infusion, 2 h after ERT) + POL-B (750,000 U q12h i.v.) + CST (inhaled 2 MU q8h)	12-day treatment. Microbiological eradication after 1-day treatment. Clinical recovery but death due to heart failure 1 mo after end of treatment.
	Adenocarcinoma and hepatocarcinoma	Blood, sputum, abdominal wound	KPC-producing *K. pneumoniae*	ERT, >32; MER, >32; IMI, >32; CST (not determined)	ERT (0.5 g q24h i.v.) + DOR (0.5 g q8h i.v., 2 h after ERT) + POL-B (750,000 U q12h i.v.)	10-day treatment. Microbiological eradication in sputum and abdominal wound after 5 days of treatment. Relapse 10 days after end of treatment in blood cultures but not in sputum sample
Camargo et al. (present case article), United States	Intestinal transplant	Abdominal wound, blood, urine, CVC	KPC-producing *K. pneumoniae*	ERT R, MER R, IMI R; CST, 0.19–1; CAZ-AVI, ≤4	ERT (1 g q24h i.v.) + MER (1 g q12h, 2 h after ERT) + CST (750,000 U q12h)	12-day treatment (adjusted to renal function). Initial response but breakthrough bacteremia after 12 days of treatment. CST resistance development (MIC, 12 μg/ml).

CR-KP tedavi çalışmaları

Yazar (hasta sayısı)	Çalışma	TGC n=7	AG n=8	CARB n=15	CARB+ n=4	POL n=7	POL+ n=11	CEF n=5
Weisenberg et al (21)	Olgu serisi	S(5), F(1)	S(3)	S(5), F(6)	F(1)			
Maltezou et al (10)	Olgu serisi		S(1)				S(7),F(2)	
Daly et al (1)	Olgu	F(1)						
Nadkarni et al (4)	Olgu		S(1)			S(1)F2		
Endimiani et al (2)	Olgu		S(1)	F(1)				
Bennet et al (1)	Olgu		F(1)					
Endimiani et al (2)	Olgu		F(1)			F(1)		
Lomaestrol et al (1)	Olgu			S(1)				
Wei et al (1)	Olgu			F(1)				
Villegas et al (1)	Olgu			F(1)				
Bradfort et al (4)	Olgu				S(3)		S(1)	
Villegas et al (2)	Olgu					F(2)		F(1)
Marschall et al (3)	Olgu							S(2),F(1)
Tibbets et al (1)	Olgu							S(1)
Mendes et al (1)	Olgu							S(1)

15 makale, 55 hasta

TGC (%71), AG (%75), POL+ (%75)

CARB (%40), POL (%14)

Fosfomisin

- İnvitro sinerji:
  - İmipenem, meropenem, kolistin, and tigesiklin
  - *A.baumannii, K.pneumoniae, P.aeruginosa*

Wei W, et al. J Chemother. 2016
Evren E, et al. Diagn Microbiol Infect Dis. 2013
Corvec S, et al. Antimicrob Agents Chemother. 2013

Antimicrob Agents Chemother. 2014 Sep;58(9):5598-601. doi: 10.1128/AAC.02435-13. Epub 2014 Jun 30.

Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections.

Sirijatuphat R[1], Thamlikitkul V[2].

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Abstract

Ninety-four patients infected with carbapenem-resistant Acinetobacter baumannii were randomized to receive colistin alone or colistin plus fosfomycin for 7 to 14 days. The patients who received combination therapy had a significantly more favorable microbiological response and a trend toward more favorable clinical outcomes and lower mortality than those who received colistin alone. (This study has been registered at ClinicalTrials.gov under registration no. NCT01297894.).

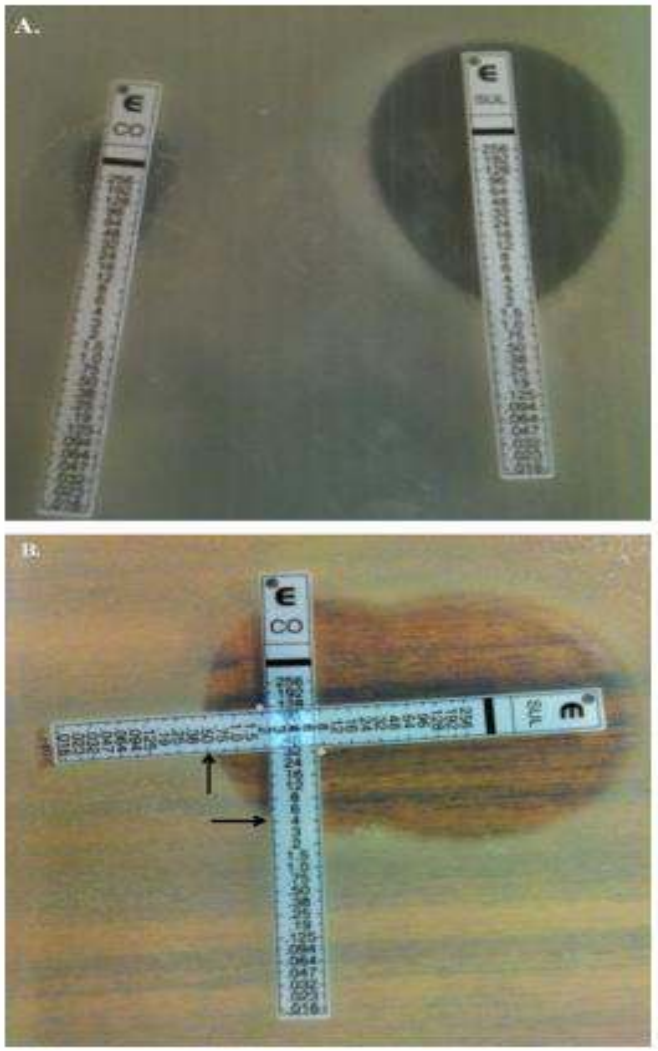
Sulbaktam

- Sulbaktam, dirençli *A.baumanni*'ye en etkili beta laktamaz inhibitörü
  - Serin beta laktamazlar
- Karbapenem dirençli

Synergistic activity of sulbactam combined with colistin against colistin-resistant *Acinetobacter baumannii*

- Kolistin dirençli *A.baumanni* (MİK=32), sulbaktam (MİK=2) iken, sinerjik aktivite
  - MİK düzeylerinde düşüş

  (32 → 4 ve 2 → 0.5)
- Direnci önlemede etkili olabilir?



Kempf M, et al, Int J Antimicrob Agents. 2012

Infection (2014) 42:37–42
DOI 10.1007/s15010-013-0495-y

CLINICAL AND EPIDEMIOLOGICAL STUDY

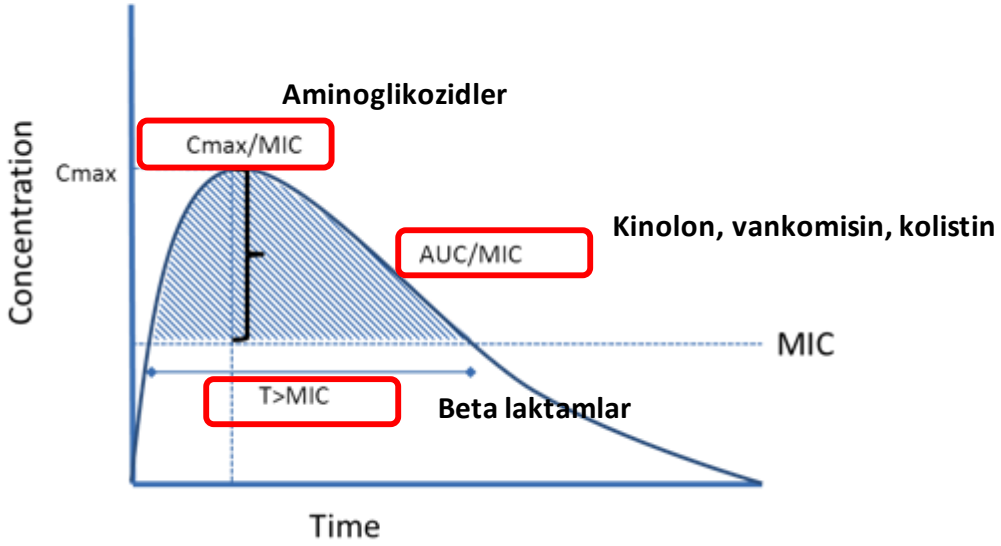
Comparison of colistin and colistin/sulbactam for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia

G. Kalin · E. Alp · A. Akin · R. Coskun · M. Doganay

On the fifth day of therapy	Colistin ($n = 52$), n (%)	Colistin/sulbactam ($n = 37$), n (%)	p
Good response	21 (40.4)	16 (43.2)	0.84
Poor response	31 (59.6)	21 (56.8)	
On the 14th day of therapy	**Colistin ($n = 47$), n (%)**	**Colistin/sulbactam ($n = 35$), n (%)**	**p**
Clinical cure	14 (29.8)	14 (40)	0.50
Clinical failure	33 (70.2)	21 (60)	
Bacteriological clearance	34 (72.3)	30 (85.7)	0.28
Bacteriological failure	13 (27.7)	5 (14.3)	
Length of ICU stay (mean ± SD)	42.33 ± 33.03	37.73 ± 24.29	0.81
Mortality	27 (51.9)	27 (73)	0.53[a]

Farmakodinami

- YBÜ'lerinde empirik tedaviyi seçerken en iyi farmakodinamiği (FD) sağlayacak dozlamayı seçmek gerekir
- İnvivo FD'nin belirlenmesinde
  - Enfeksiyon alanındaki serbest antibiyotik konsantrasyonu
  - Enfeksiyon alanında hedef patojen üzerinde antibakteriyal etki (MİK, MBK)



High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

Clinical Infectious Diseases 2012;54(12):1720–6

- Kolistin hala en etkin
- Konsantrasyon bağımlı bakterisidal etki
- Hayatı tehdit eden şiddetli enfeksiyonlarda yüksek doz ve uzamış aralıklarla kullanımı ile klinik kür yüksek, renal toksisite az

Variable	CMS Response[a]	No CMS Response
Age (years), mean ± SD	62 ± 18	76 ± 3
Charlson comorbidity index, mean ± SD	2 (1.5)	3.2 (2.2)[b]
Surgical admission, No. (%) of patients	8/20 (40)	4/5 (80)
APACHE II score, mean ± SD	18 ± 6	25 ± 7[b]
SOFA score, mean ± SD	7.6 ± 2	9.1 ± 2
ICU LOS (days)	56 (30–85)	75 (52–86)
ICU mortality, No. (%) of patients	5/20 (25)	5/5 (100)[b]
Infectious episodes, No. (%) of cases	23/28 (82.1)	5/28 (17.9)
Onset time of infection (days)	22 (12–47)	42 (23–54)
BSI, No. (%) of cases	13/23 (56.5)	5/5 (100)
BSI-associated pathogens, No. of isolates		
Acinetobacter baumannii	6	2
Klebsiella pneumoniae	6	3
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	13/13 (100)	0/5[b]
VAP, No. (%) of cases	10/23 (43.5)	0/5
VAP-associated pathogens, No. of isolates		
Acinetobacter baumannii	5	0
Klebsiella pneumoniae	4	0
Pseudomonas aeruginosa	1	0
Bacteriological clearance, No. (%) of cases	4/10 (40)	0/5 (0)
Clinical presentation, No. (%) of cases		
Severe sepsis	16/23 (69.5)	0/5 (0)[b]
Septic shock	7/23 (30.5)	5/5 (100)[b]
Daily CMS dose (MU/d)	8.5 (7.3–9)	7.7 (5–8.5)
Cumulative CMS dose (MU/course)	91 (61–122)	105 (17–142)
CMS monotherapy, No. (%) of courses	12/23 (52.2)	2/5 (40)
CMS treatment duration (days)	11 (10–14.5)	15.5 (7–21)

Monte Carlo simülasyonu

- Farklı dozlama ve hedefler olduğunda sonuç nasıl değişir?
- Bilgisayar ortamında simülasyonu
- Zelenitsky et al, antibiyotiklerin yüksek dozda ve uzamış infüzyonla verilmesi

J Antimicrob Chemother 2011; **66**: 343–349
doi:10.1093/jac/dkq348 Advance Access publication 5 October 2010

Journal of Antimicrobial Chemotherapy

Pharmacodynamics of empirical antibiotic monotherapies for an intensive care unit (ICU) population based on Canadian surveillance data

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J Antimicrob Chemother
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Journal of Antimicrobial Chemotherapy

Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients

Jason A. Roberts[1–3], Carl M. J. Kirkpatrick[4] and Jeffrey Lipman[1,2]*

Kümülatif hedefe erişim (CTA)

Antibiotic	Dose	>50% $fT_{>MIC}$ CTA (excluding MRSA)	effect	>75% $fT_{>MIC}$ CTA (excluding MRSA)	effect	100% $fT_{>MIC}$ CTA (excluding MRSA)	effect
Meropenem	**1 g every 8 h (*t*′ 0.5 h)**	**0.82 (0.88)**		**0.75 (0.80)**		**0.62 (0.66)**	
	1 g every 8 h (*t*′ 3 h)	0.85 (0.91)	+	0.80 (0.86)	+ (++)	0.73 (0.78)	+++
	2 g every 8 h (*t*′ 0.5 h)	0.85 (0.91)	+	0.79 (0.84)	+	0.69 (0.74)	++
	2 g every 8 h (*t*′ 3 h)	0.87 (0.93)	+	0.83 (0.89)	++	0.77 (0.82)	+++
Piperacillin/tazobactam	**3.375 g every 6 h (*t*′ 0.5 h)**	**0.79 (0.84)**		**0.60 (0.64)**		**0.36 (0.39)**	
	3.375 g every 6 h (*t*′ 3 h)	0.84 (0.90)	+ (++)	0.79 (0.84)	+++	0.63 (0.67)	++++
	4.5 g every 6 h (*t*′ 0.5 h)	0.80 (0.86)	+	0.65 (0.70)	+ (++)	0.42 (0.45)	++
	4.5 g every 6 h (*t*′ 3 h)	0.84 (0.90)	+ (++)	0.81 (0.87)	++++	0.67 (0.72)	++++
Cefepime	**2 g every 12 h (*t*′ 0.5 h)**	**0.81 (0.87)**		**0.74 (0.79)**		**0.62 (0.66)**	
	2 g every 12 h (*t*′ 3 h)	0.82 (0.88)	+	0.77 (0.82)	+	0.68 (0.73)	++
	2 g every 8 h (*t*′ 0.5 h)	0.85 (0.91)	+	0.81 (0.87)	++	0.78 (0.83)	+++
	2 g every 8 h (*t*′ 3 h)	0.86 (0.92)	+	0.83 (0.89)	++	0.80 (0.86)	+++
Ceftobiprole	**500 mg every 8 h (*t*′ 2 h)**	**0.90 (0.89)**		**0.86 (0.85)**		**0.76 (0.75)**	
	1 g every 8 h (*t*′ 4 h)	0.93 (0.92)	+	0.91 (0.90)	+	0.88 (0.87)	+++

Daha fazla hedefe ulaşmak, daha az duyarlı (*P.aeruginosa*) patojenleri kapsamak

		MSSA		*E. coli*		*P. aeruginosa*	
Antibiotic	Dose	CTA	effect	CTA	effect	CTA	effect
Meropenem	**1 g every 8 h (t' 0.5 h)**	**0.95**		**0.96**		**0.57**	
	1 g every 8 h (t' 3 h)	0.99	+	0.99	+	0.71	+++
	2 g every 8 h (t' 0.5 h)	0.97	+	0.98	+	0.68	+++
	2 g every 8 h (t' 3 h)	1.00	+	1.00	+	0.79	++++
Piperacillin/tazobactam	**3.375 g every 6 h (t' 0.5 h)**	**0.86**		**0.70**		**0.32**	
	3.375 g every 6 h (t' 3 h)	0.99	+++	0.92	++++	0.61	++++
	4.5 g every 6 h (t' 0.5 h)	0.89	+	0.75	+	0.39	++
	4.5 g every 6 h (t' 3 h)	0.99	+++	0.94	++++	0.68	++++
Cefepime	**2 g every 12 h (t' 0.5 h)**	**0.88**		**0.94**		**0.61**	
	2 g every 12 h (t' 3 h)	0.95	++	0.96	+	0.69	++
	2 g every 8 h (t' 0.5 h)	0.99	+++	0.98	+	0.83	++++
	2 g every 8 h (t' 3 h)	1.00	+++	0.99	+	0.88	++++
Ceftobiprole	**500 mg every 8 h (t' 2 h)**	**0.98**		**0.93**		**0.54**	
	1 g every 8 h (t' 4 h)	1.00	+	0.95	+	0.79	++++

Etkenler üzerinde > 0.9'un üzerinde kümülatif hedef erişimi sağlamak için hepsinde uzamış infüzyon ve/veya yüksek doz gerekiyor

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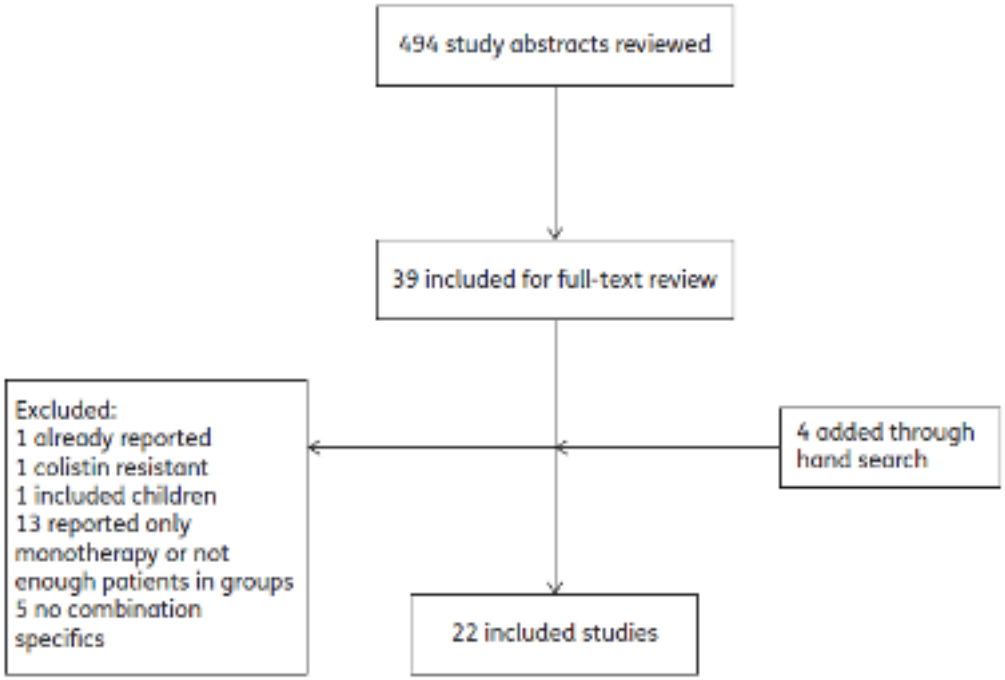
Journal of Antimicrobial Chemotherapy

Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis

Oren Zusman[1]*, Sergey Altunin[2,3]†, Fidi Koppel[2], Yael Dishon Benattar[2,4], Habip Gedik[5] and Mical Paul[2,3]

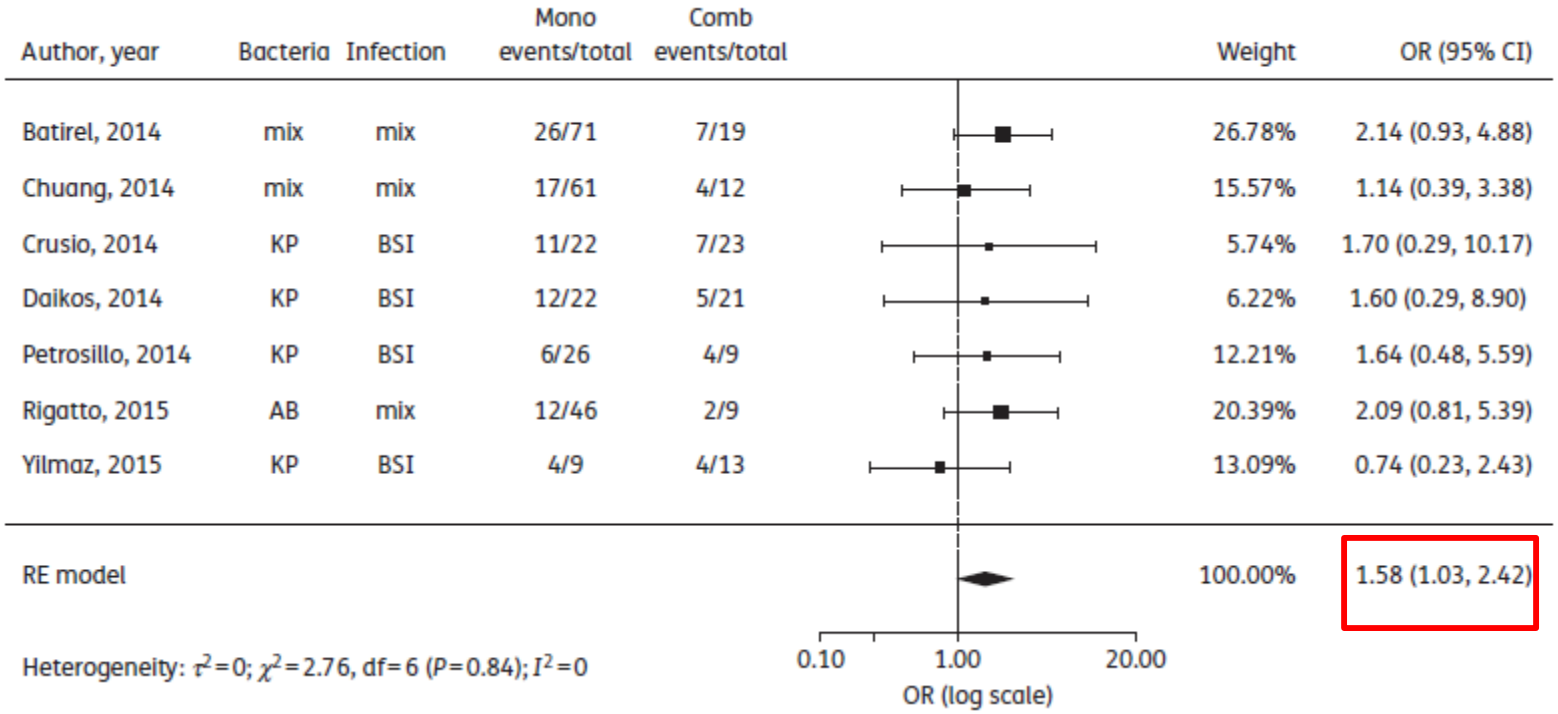


CR-GNB mono/ kombine tedavi çalışmaları 2010-2016

Author	Publication year	Study years	Location	Study type	Bacteria	Carbapenemase	Carbapenem MIC (mg/L)	Polymicrobial	Setting	Infection type	Polymyxin	Combination with	Number of patients
Falagas	2010	2000–07	Greece	Ret	AB CRE PA	NA	NA	NA	mostly ICU	any	colistin	carbapenem	104
Petrosillo	2014	2010–11	Italy, Turkey	Ret	AB KP PA	NA	NA	yes	ICU	BSI VAP UTI SSTI IAI	colistin	vancomycin	103
												tigecycline	73
												carbapenem	82
Mouloudi	2010	2007–08	Greece	nested CC	KP	blaVIM blaKPC blaSHV blaTEM blaCTX-M	>64	NA	ICU	BSI	colistin	aminoglycoside	36
Nguyen	2010	2004–08	USA	Ret	KP	KPC-2 KPC-3	>8	no	mix	BSI	polymyxin B	tigecycline	22
Zarkotou	2011	2008–10	Greece	Ret	KP	blaKPC	NA	no	mostly ICU	BSI	polymyxin B	tigecycline	16
Ku	2012	2009	USA	Ret	AB CRE	blaKPC	NA	yes	mix	BSI HAP UTI SSTI	colistin	tigecycline	90
Simsek	2012	2008–11	Turkey	Ret	AB	NA	NA	NA	mix	BSI VAP SSTI	colistin	rifampicin	23
Tumbarello	2012	2010–11	Italy	Ret	KP	blaKPC2 blaKPC3	NA	NA	mix	BSI	colistin	tigecycline	45
												tigecycline + meropenem	38
Tumbarello	2012	2010–11	Italy	Ret	KP	NA	NA	NA	mix	BSI	colistin	tigecycline + meropenem	38
Durante-Mangoni	2013	2008–11	Italy	RCT	AB	blaOXA-51-like	≥16	yes	ICU	HAP VAP BSI IAI	colistin	rifampicin	209
Aydemir	2013	2011–12	Turkey	RCT	AB	NA	NA	no	ICU	VAP	colistin	rifampicin	43
Garnacho-Montero	2013	2008–11	Spain	Ret	AB	NA	NA	no	ICU	VAP BSI	colistin	vancomycin	57
Batirel	2014	2009–12	Turkey	Ret	AB	NA	NA	yes	mix	BSI	colistin	carbapenem	138
												sulbactam	105
Chuang	2014	2009–10	Taiwan	Ret	AB	NA	NA	no	ICU	HAP VAP	colistin	carbapenem	119
Kalin	2014	2011	Turkey	Ret	AB	NA	NA	NA	ICU	VAP	colistin	sulbactam	82
Daikos	2014	2009–10	Greece	Ret	KP	KPC-2 VIM-1	>8	NA	mix	BSI	colistin	tigecycline	33
												aminoglycoside	33
												both	39
Kontopidou	2014	2009–10	Greece	Ret/Pro	KP	KPC VIM	NA	NA	ICU	VAP BSI UTI SSTI IAI	colistin	aminoglycoside	43
												tigecycline	35
												both	30
Lopez-Cortes	2014	2010	Spain	Ret	AB	NA	NA	yes	mix	HAP UTI BSI IAI SSI	colistin	tigecycline	55
Crusio	2014	2009–10	USA	Pro	KP AB PA	NA	NA	no	mostly ICU	BSI	polymyxin B	carbapenem	56
Sirijatuphat	2014	2010–11	Thailand	RCT	AB	NA	NA	yes	mix	HAP VAP UTI BSI IAI SSTI CNS	colistin	fosfomycin	82
Yilmaz	2015	2011–13	Turkey	Ret	AB	NA	NA	NA	ICU	VAP	colistin	carbapenem	50
												sulbactam	37
Rigatto	2015	2013–14	Brazil	Ret	AB PA	NA	>32	yes	ICU	BSI HAP VAP UTI IAI	polymyxin B	carbapenem	92
Gomez-Simmonds	2016	2006–13	USA	Ret	KP	blaKPC	>16	no	ICU	BSI	polymyxin B	tigecycline and aminoglycoside	39

Zusman et al, 2017

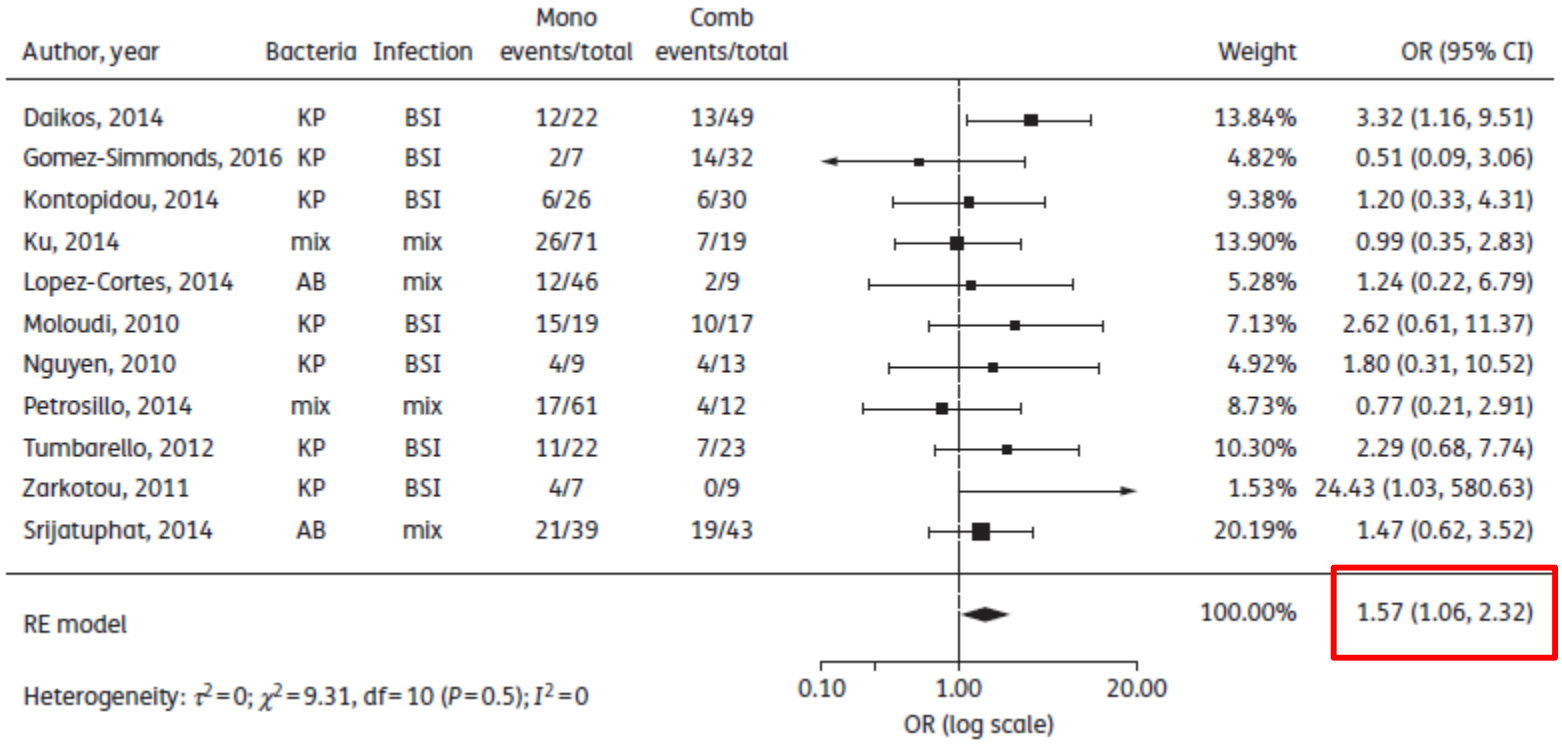
Polimiksin/karbapenem kombinasyonları



- Gözlemsel, 7 çalışma
- Mortalite için kombinasyon yönünde bir kayış var
  - Kanıt kalitesi düşük
- Klinik ve mikrobiyolojik başarı arasında fark yok

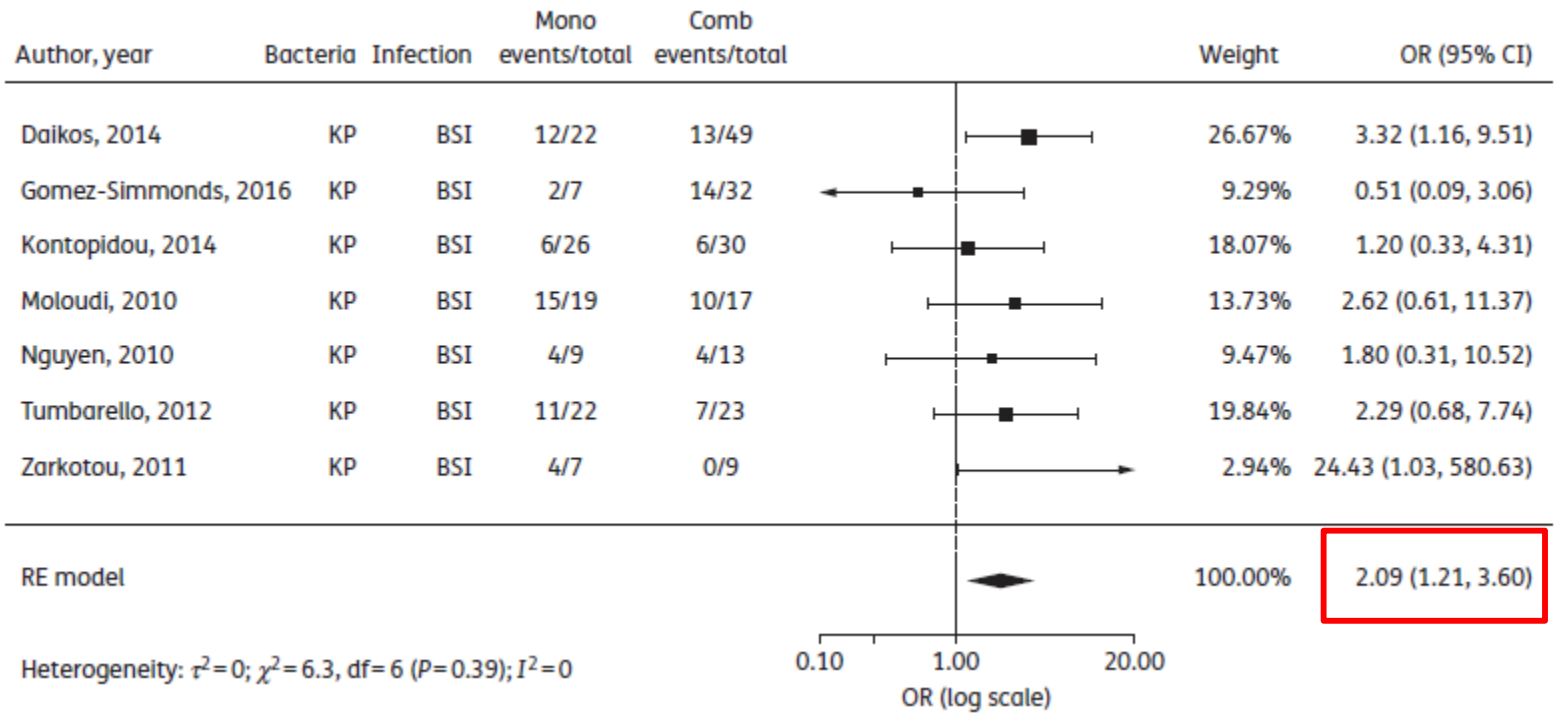
Zusman et al, 2017

Polimiksin/tigesiklin, aminoglikozid, fosfomisin kombinasyonları



Düşük kalite kanıt
Kombinasyon lehine

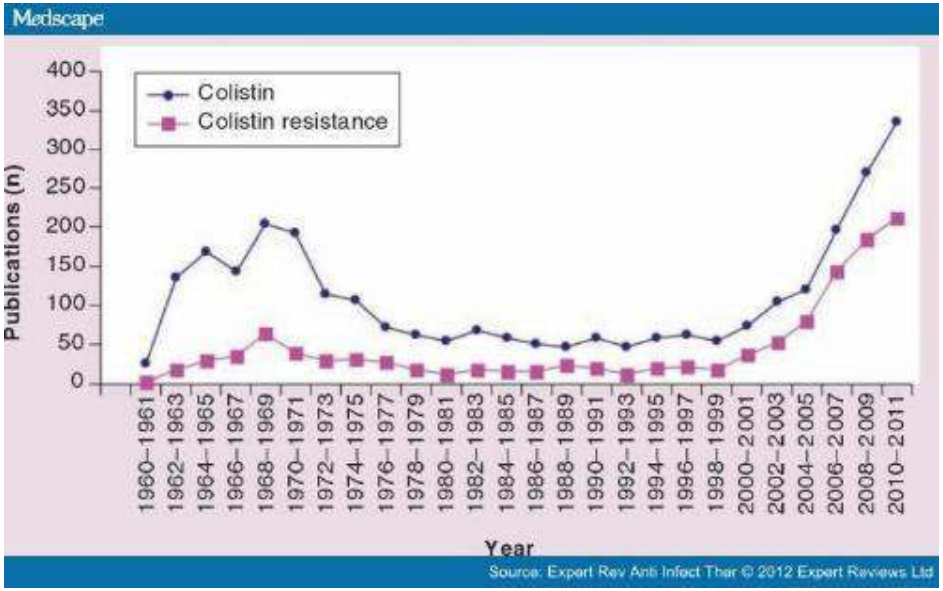
Tigesiklin, aminoglikozid sadece KP için kan dolaşımı enfeksiyonları



Yine de kombinasyonu önermek için yeterli kanıt düzeyi yok!!!

Kolistin direnci ve antibiyotik krizi

- Günümüzde bir çok ülkeden yapılan yayınlar ile kolistin dirençli (ColR) suşların varlığı rapor edilmiştir



Kolistin direnci

- Yi-Yun Liu ve arkadaşları plazmid aracılığıyla taşınan *mcr-1* genini tanımladılar (2015 Kasım)
  - *2011-2014 arasında* hayvanlar, hayvansal gıda ve hastalardan izole edilen Enterobacteriaceae üyelerinde mcr-1 varlığını göstermişler

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

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Lucheng Lv, Dandan He, Hongwei Zhou, Zhen-Liang Ren-Hua Liu, Jianzhong Shen

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Methods The *mcr-1* gene in *E coli* strain SHP45 was identified by whole plasmid sequencing and subcloning. MCR-1 mechanistic studies were done with sequence comparisons, homology modelling, and electrospray ionisation mass spectrometry. The prevalence of *mcr-1* was investigated in *E coli* and *Klebsiella pneumoniae* strains collected from five provinces between April, 2011, and November, 2014. The ability of MCR-1 to confer polymyxin resistance in vivo was examined in a murine thigh model.

Mcr-1 geninin hareketli bir plazmid tarafından taşınıyor olması önemli bir tehlikeye işaret etmektedir

PLOS | ONE

RESEARCH ARTICLE

Antimicrobial Combinations against Pan-Resistant *Acinetobacter baumannii* Isolates with Different Resistance Mechanisms

Gleice Cristina Leite[1,2], Maura Salaroli Oliveira[1,3], Lauro Vieira Perdigão-Neto[1,2,3], Cristiana Kamia Dias Rocha[2], Thaís Guimarães[4], Camila Rizek[2], Anna Sara Levin[1,2,3], Silvia Figueiredo Costa[1,2,3]*

Antibiotic	Antibiotic tested in combination	Colistin-Susceptible (n = 13)		Colistin-Resistant (n = 7)	
		*Synergism (%)		*Synergism (%)	
		**FICI	2-Well	**FICI	2-Well
Colistin					
	Imipenem	0	15	0	**100**
	Tigecycline	0	15	0	0
	Gentamycin	0	23	0	0
	Amikacin	0	15	0	14
	Meropenem	0	23	0	**100**
	Vancomycin	0	**69**	14	**100**
	Rifampicin	23	**77**	**100**	**100**
	Fosfomycin	0	54	0	0
Imipenem					
	Tigecycline	0	31	0	43
	Gentamycin	0	54	0	29
	Amikacin	0	46	0	14
	Vancomycin	0	0	0	0
	Rifampicin	0	39	0	0
	Fosfomycin	0	23	0	0
Tigecycline					
	Gentamycin	0	8	0	29
	Amikacin	0	46	0	14
	Meropenem	0	8	0	29
	Vancomycin	0	8	0	0
	Rifampicin	0	0	0	0
	Fosfomycin	0	0	0	0
Fosfomycin					
	Gentamycin	0	**77**	0	43
	Amikacin	0	**100**	0	**71**
	Meropenem	0	23	0	29
	Vancomycin	0	23	0	14
	Rifampicin	0	39	0	0

PLOS | ONE

RESEARCH ARTICLE

Antimicrobial Combinations against Pan-Resistant *Acinetobacter baumannii* Isolates with Different Resistance Mechanisms

Gleice Cristina Leite[1,2], Maura Salaroli Oliveira[1,3], Lauro Vieira Perdigão-Neto[1,2,3], Cristiana Kamia Dias Rocha[2], Thaís Guimarães[4], Camila Rizek[2], Anna Sara Levin[1,2,3], Silvia Figueiredo Costa[1,2,3]*

İnvitro sinerjik olmasına rağmen vankomisin kombinasyonları başarılı değil

	Patients N = 18	Surviving during treatment N = 6	Death during treatment N = 8
Age (years), mean (range)	43 (15–68)	38 (16–59)	44 (15–69)
Female	6	5	1
Underlying diseases			
Hematologic cancer	4	0	4
Cirrhosis	3	3	0
Abdominal surgery	2	1	1
Trauma	2	2	0
Kidney transplant	1	1	0
Others	5	2	3
Intensive Care Unit	6	4	2
Apache II, median	16	15	13
Colonization	3	-	-
No treatment	4*	-	-
Infection	14	6	8
Blood	13	6	7
Tracheal secretion	1	-	1
Treated *A. baumannii* infection	14	6	8
In vitro synergism with vancomycin plus colistin by time-kill	14	6	8
In vitro synergism with vancomycin plus imipenem by time-kill	9	4	5
Received vancomycin plus *A. baumannii* treatment	7	2	5

In vitro synergism of combinations of colistin with selected antibiotics against colistin-resistant Acinetobacter baumannii

Isolates	Colistin + Netilmicin		Colistin + Sulbactam		Colistin + Vancomycin	
	FICI	Result	FICI	Result	FICI	Result
1	2	indifference	0.562	indifference	0.126	synergy
2	0.255	synergy	0.265	synergy	0.257	synergy
3	2	indifference	0.507	indifference	0.515	indifference
4	0.562	indifference	0.187	synergy	0.140	synergy
5	0.531	indifference	0.375	synergy	0.046	synergy
6	0.507	indifference	0.281	synergy	0.281	synergy
7	0.532	indifference	0.187	synergy	0.281	synergy
8	1.25	indifference	0.75	indifference	0.124	synergy
9	1.015	indifference	1.031	indifference	0.253	synergy
10	1.25	indifference	1.5	indifference	0.140	synergy

Percin D, et al. GMS Hygiene and Infection Control 2014;9:1-5

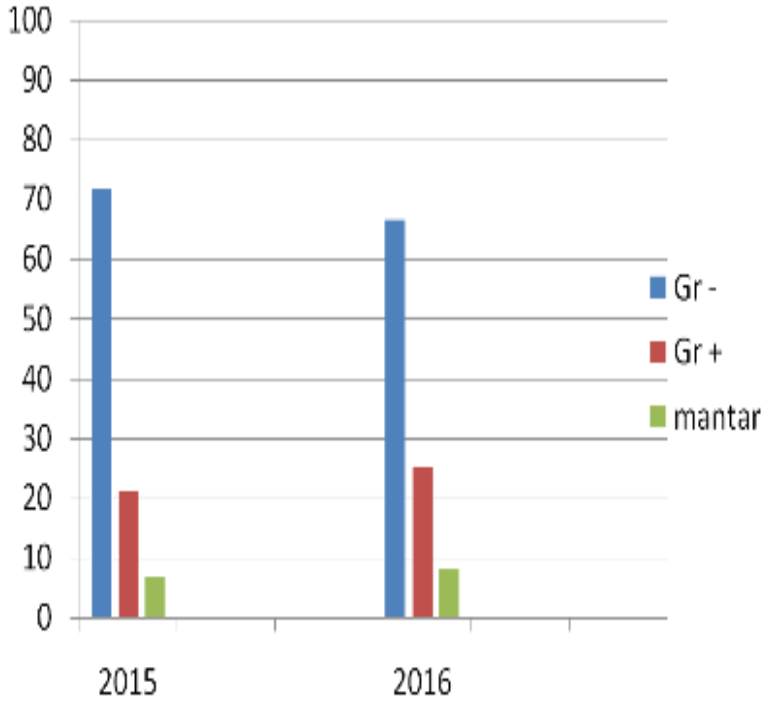
Kolistin dirençli gram negatifler ciddi mortalite ile ilişkili
Tedavi yaklaşımları ile ilgili invitro ve klinik çalışmalara gerek var

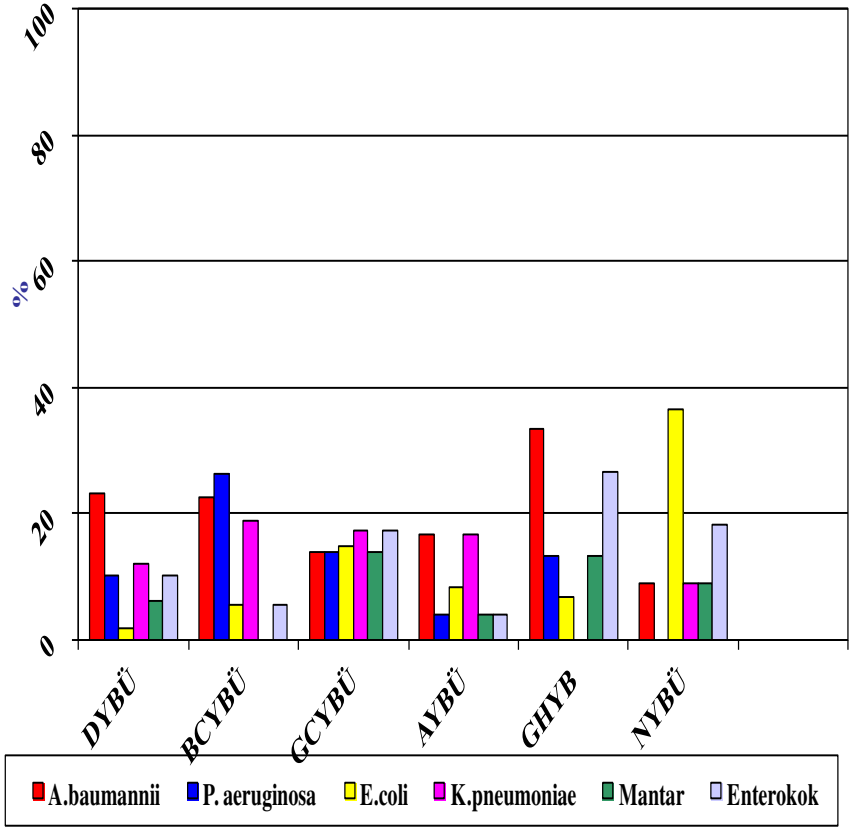
Özet olarak

- Farklı çalışmalarla farklı sonuçlar
- Üstün bulunan ve önerilen bir kombinasyon henüz yok
- Lokal epidemiyolojik veriler ışığıda
- Kolistin direnci kapıda
  - Rasyonel antibiyotik kullanım
  - Erken tespiti ve enfeksiyon kontrolü

Teşekkürler.....

Erciyes Üniversitesi Hastaneleri YBÜ Nozokomiyal Enfeksiyon Epizotlarından Sorumlu Mikroorganizmalar





EÜ Enfeksiyon Kontrol Kurulu Sürveyans verileri

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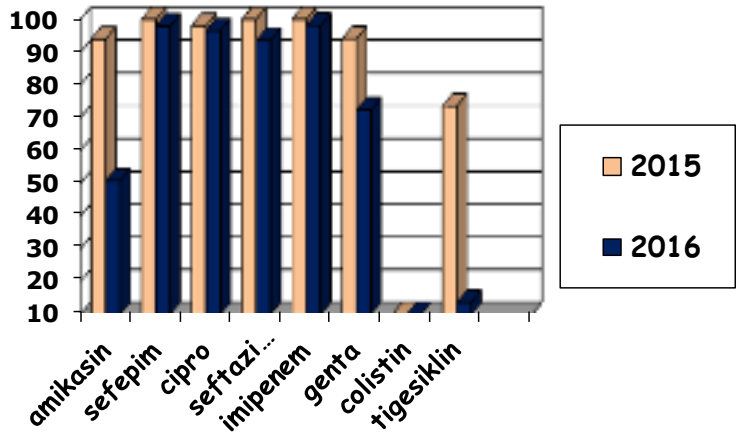
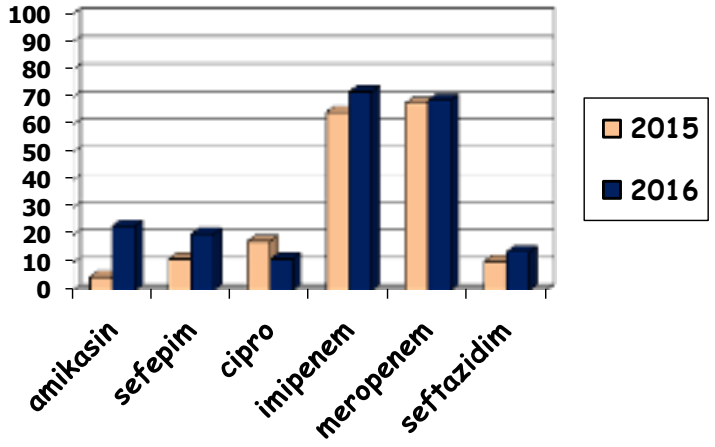
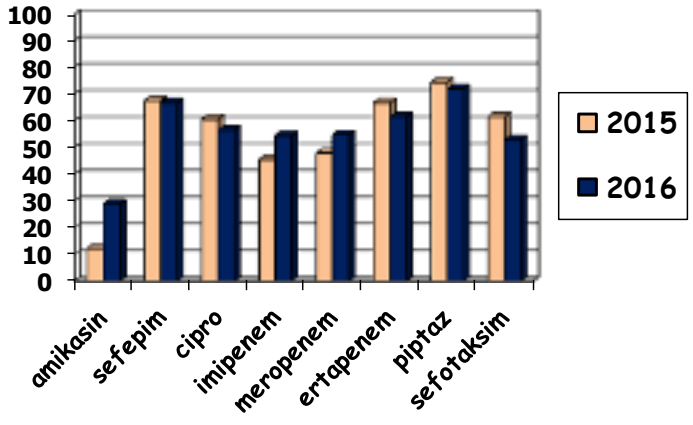
A.baumannii Antibiyotik Direnci



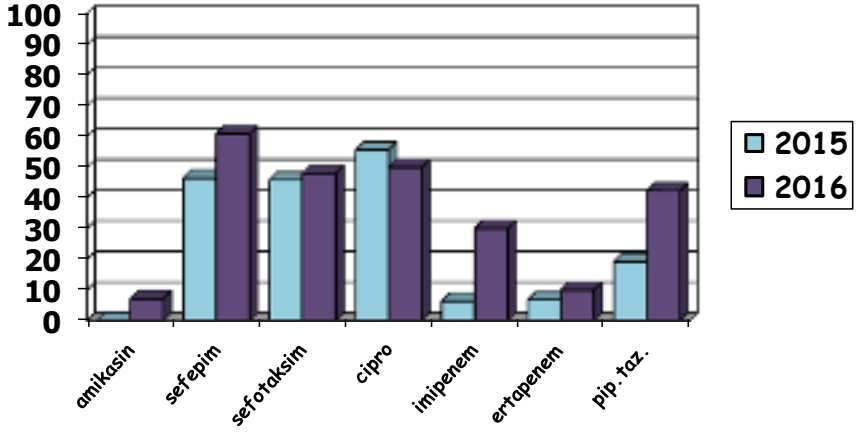
P.aeruginosa Antibiyotik Direnci



K.pneumoniae Antibiyotik Direnci



E.coli Antibiyotik Direnci



EÜ Enfeksiyon Kontrol Kurulu Sürveyans verileri

A.baumannii (n=383)
2016- 2017

Antibiyotik (MİK>R)	MİK (en düşük)	MİK (en yüksek)	Ortanca
Tigesiklin (IE)	0.5	8	1
Meropenem (8)	<0.25	≥16	≥16
İmipenem (8)	≤0.25	≥16	≥16
Gentamisin (4)	≤1	≥16	≥16
Amikasin (16)	≤2	≥64	≥16
Siprofloksasin (1)	≤0.25	≥4	≥4

Erciyes Üniversitesi Hastaneleri- Kolistin dirençli GNB

1. Kolistin dirençli GNB'ler
2. Mcr-1 gen varlığı (PCR)
3. Klonal yakınlık (PFGE)
    - ColR *K.pneumoniae*
    - ColR *A.baumannii*

Bakteriler	n(%)
A.baumannii	57 (46.7)
K.pneumoniae	51 (41.8)
P. aeruginosa	5 (4.1)
Gram (-) basil	6 (4.9)
Acinetobacter spp.	3 (2.5)
Toplam	122 (100)

2011 yılı itibari ile E-test ile MİK bakıldı (n=122)

Ortalama MİK değeri 4 (4-64) olarak bulundu

YBÜ'nde takip edilen, n=88 (%72.1)

122 hastanın %43.4'ü ColR geliştirmeden önce kolistin tedavisi alıyordu

Table 1. The reasons for previous colistin use before the isolation of ColR strains

	ColR strains		
	A. baumannii (n=31)*	*K. pneumoniae* (n=19)*	*P. aeruginosa* (3)*
Reason for colistin use			
Empirical	7	5	2
Infection caused by carbapenem resistant			
ColS *A. baumanni*	22	8	0
ColS *K. pneumoniae*	0	6	0
ColS *E. coli*	1	0	0
ColS *P. aeruginosa*	0	0	1
GNB	1	0	0

Gundogdu A, Ulu Kilic A et al.
Yayınlanmamış veri

Table 2. The risk factors candidates for ColR *K. penumoniae* isolates

Variables	ColR (n=51)	ColS (n=60)	*p*
Median age (min-max)	59 (19-84)	36 (0-93)	**0.020**
Previous hospitalisation day (min-max)	51 (1-116)	60 (1-153)	**0.033**
Transfer from an other unit	15	12	0.274
Transfer from another institution	1	3	0.623
Underlying diseases			
Diabetes mellitus	8	3	0.252
Chronic renal failure	9	3	0.620
Chronic heart failure	4	1	0.178
COPD*	5	2	0.158
Previous use of antibiotics			
carbapenems	22	13	**0.024**
beta-lactams	31	33	0.568
glycopeptides	20	10	**0.010**
colistin	19	8	**0.004**
tygesiclin	4	1	0.178
Clinical specimens			
blood	14	19	0.681
urine	8	13	0.474
ETA	5	9	0.568
wound	8	8	0.790
dren	4	2	0.411
absess	5	1	0.092
others	7	8	1.000

Gundogdu A, Ulu Kilic A et al.
Yayınlanmamış veri

Table 3. The risk factor candidates for ColR *A. baumannii* isolates

Variables	ColR (n=60)	ColS (n=60)	*p*
Median age (min-max)	53.5 (0-86)	56.5 (0-95)	**0.429**
Previous hospitalisation day (min-max)	73 (1-144)	47 (3-88)	**0.000**
Transfer from an other unit	18	25	0.253
Transfer from another institution	0	4	0.119
Underlying diseases			
Diabetes mellitus	8	11	0.618
Chronic renal failure	13	11	0.820
Chronic heart failure	1	3	0.619
COPD*	8	9	1.000
Previous use of antibiotics			
carbapenems	39	20	**0.001**
beta-lactams	32	36	0.581
glycopeptides	23	16	0.242
colistin	31	12	**0.001**
metronidazol	3	0	0.244
macrolid	1	3	0.619
tygesiclin	6	2	0.163
linezolid	3	1	0.364
Clinical specimens			
blood	10	20	0.057
urine	8	1	**0.032**
ETA	10	15	0.369
wound	4	5	1.000
dren	1	2	1.000
BOS	1	4	0.364
BAL	11	10	1.000
others	15	8	0.496

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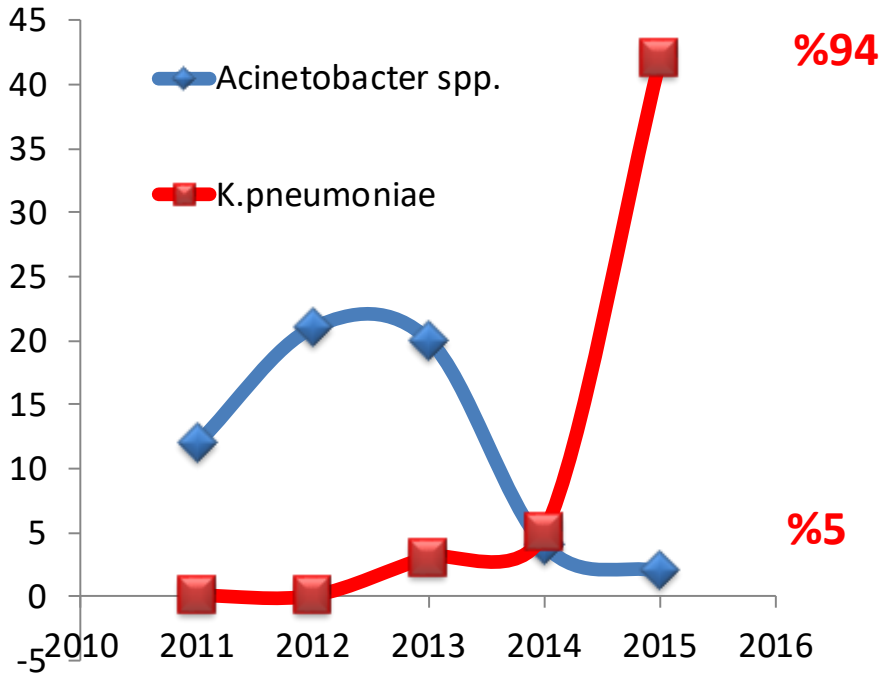
Yayınlanmamış veri

Erciyes Üniversitesi Hastaneleri- Kolistin dirençli GNB



Bakteriler	No
K. pneumoniae	37
A. baumannii	5
A. junii	1
C. braakii	1
P. aeruginosa	1
Klinik örnekler	
Kan	13
İdrar	9
Yara & Abse	6
ETA	5
Doku	3
Kateter	2
Safra	2
Nefrostomi	2
BAL	1
Balgam	1
Kolistin kullanımı	
yok	18
1-7 gün	8
7-14 gün	6
14-21 gün	6
>21	9

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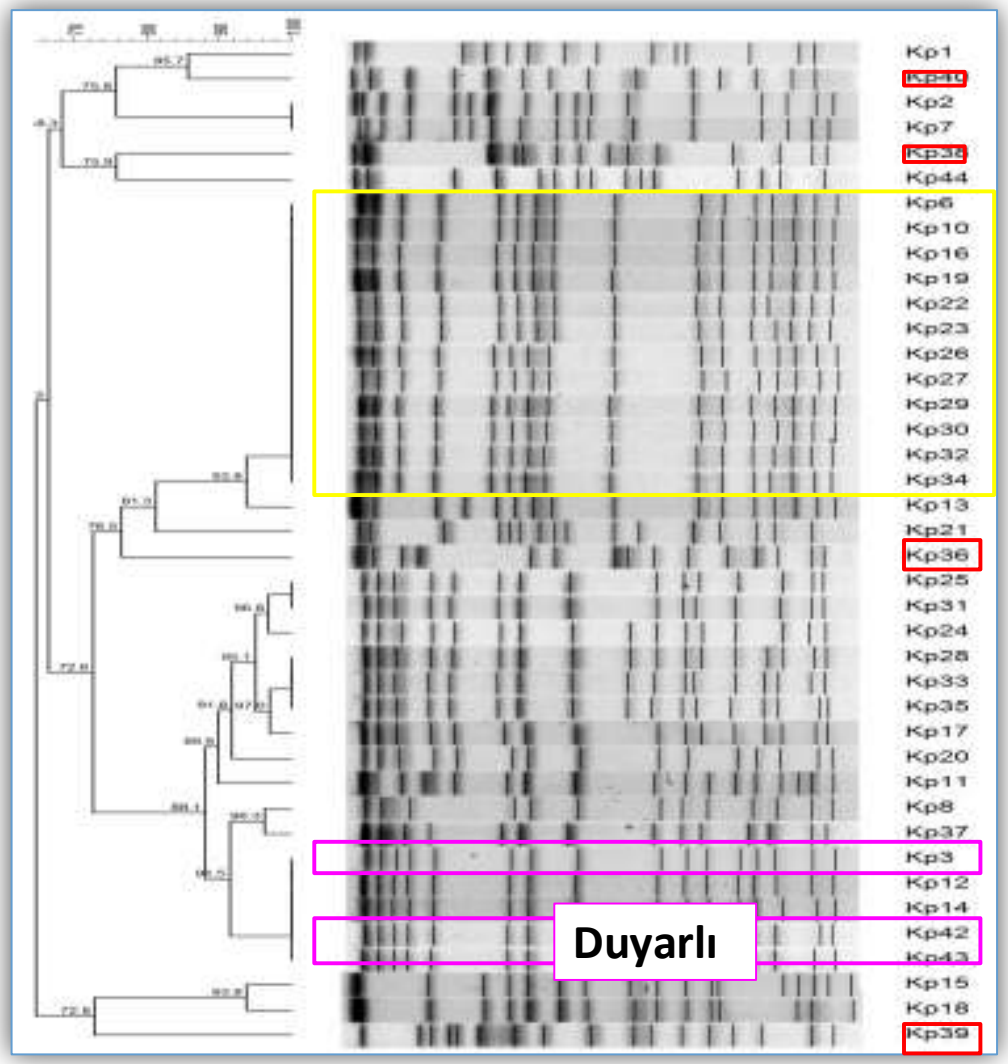
K. pneumoniae PFGE sonuçları (2014 Nisan- 2016 Mart)



1 major 4 minor klonda

Aynı hastadan 3 aylık zaman diliminde izole edilen 2 ColS (**Kp42 ve Kp43**) ve bir ColR K. pneumoniae (**Kp3**) suşu arasında %100 benzerlik bulundu

2016 yılında izole edilmiş olan 5 ColR suşunun 4'ü (**Kp36, Kp38, Kp39 ve Kp40**) her hangi bir suşla klonal yakınlık göstermedi
(en benzer suşla arasında %75 yakınlık bulundu)

2 ayrı hastadan tedavi öncesi izole edilen 3 adet ColS *K. pneumoniae* suşu da klonal yakınlık çalışmasına dahil edilmiştir

Kolistin dirençli GNB-Sonuçlar

- Bütün ColR izolatlar mcr-1 için negatifti
- Tigesiklin duyarlılığı
  - *A.baumannii* (%100)
  - *K.pneumoniae* (%81)
- Aminoglikozidler
  - *A.baumannii*, 4/6 (%67)
  - *K.pneumoniae*, 18/36 (%50)
- **Öncesinde kolistin kullanımı ~ %40**
- **Mortalitesi yüksek ~ %60**

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Isolates no	Clinical Specimens	Ward	Isolation date	MIC of colistin	PIP	TZP	CAZ	FEP	AZT	IMI	MER	AMK	GEN	CIP	LVX	TET	TGC	STX
Kp1	urine	Rad. Onk	2014	64	R	R	R	R	R	R	R	I	R	R	R	R	S	S
KP2	wound	ICU	2014	>128	R	R	R	R	R	R	R	I	S	R	R	R	R	R
KP3	ETA	ICU	2014	128	R	R	R	R	R	R	R	R	S	R	R	R	S	R
KP6	ETA	ICU	2015	32	R	R	R	R	R	R	R	I	S	R	R	R	S	R
KP7	blood	ICU	2015	128	R	R	R	R	R	R	R	I	S	R	R	R	I	R
KP8	urine	PSİ	2015	64	R	R	R	R	R	R	R	R	S	R	R	R	S	R
KP10	blood	ICU	2015	32	R	R	R	R	R	R	R	I	I	R	R	I	S	R
KP11	absses	URO	2015	128	R	R	R	R	R	R	R	I	R	R	R	R	S	S
KP12	tissue	ICU	2015	128	R	R	R	R	R	R	R	I	S	R	R	R	S	R
KP13	blood	GASTRO	2015	64	R	R	R	R	R	R	R	I	R	R	R	R	S	R
KP14	blood	HEMATO	2015	>128	R	R	R	R	R	R	R	S	S	R	R	R	S	R
KP15	absses	ICU	2015	>128	R	R	R	R	R	R	I	I	R	R	R	S	S	S
KP16	BAL	ICU	2015	64	R	R	R	R	R	R	R	I	I	R	R	R	S	S
KP17	blood	ICU	2015	128	R	R	R	R	R	R	R	R	I	R	R	R	S	R
KP18	NEFROSTO	URO	2015	128	R	R	R	R	R	R	R	I	R	R	R	I	S	S
KP19	blood	ICU	2015	32	R	R	R	R	R	R	R	I	S	R	R	R	I	R
KP20	urine	EMER	2015	32	R	R	R	R	R	R	R	I	R	R	R	R	S	R
KP21	urine	INFECT	2015	64	R	R	R	R	R	R	R	I	I	R	R	R	R	R
KP22	urine	ICU	2015	32	R	R	R	R	R	R	R	I	I	R	R	R	S	R
KP23	blood	ICU	2015	32	R	R	R	R	R	R	R	I	I	R	R	R	S	R
KP24	wound	ICU	2015	128	R	R	R	R	R	R	R	I	R	R	R	R	S	R
KP25	bile	ICU	2015	64	R	R	R	R	R	R	R	I	R	R	R	R	S	R
KP26	ETA	ICU	2015	32	R	R	R	R	R	R	R	I	S	R	R	R	S	R
KP27	ETA	ICU	2015	32	R	R	R	R	R	R	R	I	S	R	R	R	S	R
KP28	bile	ICU	2015	128	R	R	R	R	R	R	R	R	S	R	R	R	S	R
KP29	wound	ICU	2015	>128	R	R	R	R	R	R	R	I	S	R	R	R	S	S
KP30	urine	ICU	2015	>128	R	R	R	R	R	R	R	I	S	R	R	R	I	R
KP31	urine	ICU	2015	64	R	R	R	R	R	R	R	I	R	R	R	R	S	S
KP32	tissue	ICU	2015	32	R	R	R	R	R	R	R	I	S	R	R	R	S	R
KP33	wound	ICU	2015	64	R	R	R	R	R	R	R	I	R	R	R	R	S	S
KP34	blood	ICU	2015	16	R	R	R	R	R	R	R	I	S	R	R	R	S	R
KP35	sputum	ICU	2016	64	R	R	R	R	R	R	R	I	R	R	R	R	S	R
KP36	greft	EMER	2016	32	R	R	I	I	I	I	R	S	S	S	S	R	S	R
KP37	urine	HEMATO	2016	128	R	R	R	R	R	R	R	R	S	R	R	R	S	R
KP38	urine	INFECT	2016	128	R	R	I	I	I	R	I	I	S	R	R	R	I	R
KP39	blood	ICU	2016	>128	R	R	R	R	R	R	R	I	R	R	R	R	R	R
KP40	chather	ICU	2016	128	R	R	R	R	R	R	R	I	R	R	R	R	S	R

ETA; endotracheal aspirate, ICU; intensive care unit, PED; Pediatrics, MIC; minimum inhibitory concentration, TZP; piperacillin tazobactam, CAZ;ceftazidime, FEP; cefepime, AZT; aztreonam, IMI; Imipenem, MER; meropenem, AMK; amikacin, GEN; gentamicin, CIP; ciprofloxasin, LVX; levofloxacin, TET; tetracycline, TGC; tigecycline, STX; trimethoprim-sulfamethoxazole, R; resistance, S; susceptible.