Çoklu Dirençli Mikroorganizmalarda Olgu Temelli Yönetim

Prof. Dr. Halis Akalın

ÇİD - Uzlaşı Toplantısı - 2011

- *Staphylococcus aureus*
- *Enterococcus* spp.
- *Enterobacteriaceae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.

Magiorakos AP et al. Clin Microbiol Infect 2011

Table 1e. *Acinetobacter* spp.; antimicrobial categories and agents used to define MDR, XDR and PDR

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
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-sulfamethoxazole	
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam	
Polymyxins	Colistin	
	Polymyxin B	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

Criteria for defining MDR, XDR and PDR in *Acinetobacter* spp.

MDR: non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories

XDR: non-susceptible to ≥ 1 agent in all but ≤ 2 categories,

PDR: non-susceptible to all antimicrobial agents listed

WHO-Acil Yeni Antibiyotik İhtiyacı

- 2017
- Öncelik: Kritik, Yüksek, Orta
- Kritik Grup: ÇİD bakteriler
  - -Enterobacteriaceae (ESBL, CR)
  - -CR-*Acinetobacter baumannii*
  - -CR-*Pseudomonas* aeruginosa

Olgu Sunumu

- 18 yaşında erkek hasta
- 2.5 yaşından beri Hiper IgM sendromu nedeniyle takip ediliyor
- 3 haftada bir IVIG alıyor

- 3.Mayıs.2015 tarihinde ateş, sarılık, halsizlik, karın ağrısı ve ishal nedeniyle Zonguldak Bülent Ecevit Üniv. Hastanesine başvuruyor
- Meropenem + Teikoplanin
- 8.Mayıs.2015 tarihinde UÜTF ÇSH kliniğine yatırılıyor
- Ateşi ve ikteri devam eden hastada antibiyotik tedavisi Meropenem + Vankomisin şeklinde devam ediyor

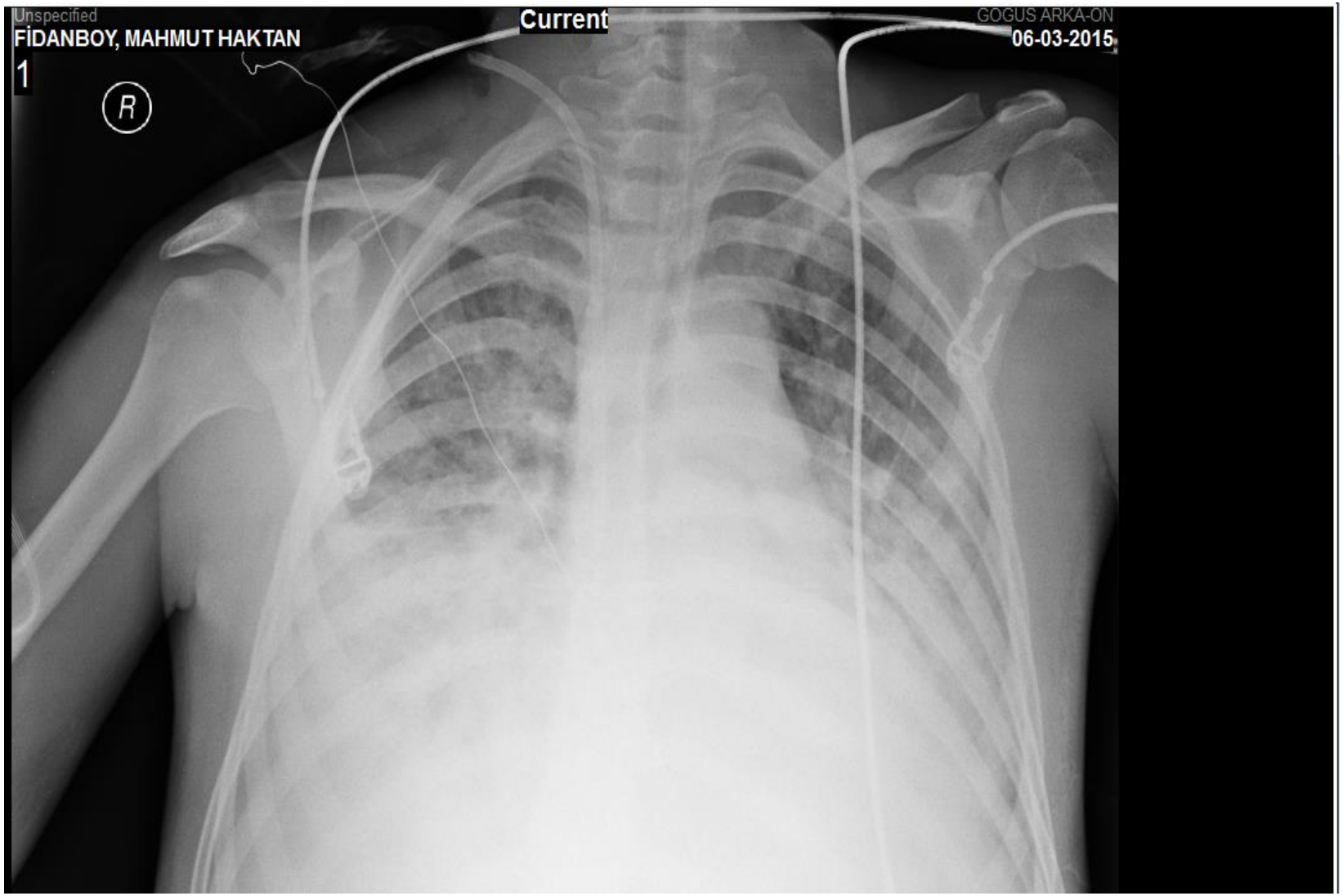
- Cilt ve skleralar ikterik
- Traube kapalı – Dalak 3 cm
- Lökosit 3337/mm^3
- Trombosit 107000/mm^3
- ALT 44 IU/L, AST 127 IU/L, TB 25 mg/dl, DB 15 mg/dl, INR 1.37
- CRP 1.2 mg/dl
- Batın USG(Dış Merkez): KC 154 mm, grade 2 hepatosteatoz, dalak 175 mm

- 10 ve 11.Mayıs.2015 Bilirubin aferezi
- 15.Mayıs.2015 KC biyopsisi:Kolestaz + Siroz + Bakır birikimi(Wilson Hastalığı?)
- MELD skoru 22, KC Transplantasyon hazırlığı
- 18.Mayıs.2015 Ateşi devam eden hastaya AmB-d başlanmış
- Otoimmün Hepatit?
- Steroid tedavisi başlanmış
- 22.Mayıs.2015 Meropenem ve Vankomisin kesilmiş

- 22.Mayıs.2015 Pnömoni tanısı ile Sefepim + Levofloksasin
- 24.Mayıs.2015 Üre:94mg/dl Kreatinin:1.02 mg/dl
- AmB-d kesilerek L-AmB ve ayrıca TMP/SMX başlanmış
- 24.Mayıs.2015 Kardiyak arrest + Solunum yetmezliği nedeniyle entübe edilerek YBÜ'de MV desteğine alınmış

- 1.Haziran.2015 BAL: GM 2.54 ve 1000 kob/ml *K.pneumoniae*
- 5.Haziran.2015 Sefepim(15) ve Levofloksasin(15) kesildi
- KC transplantasyonu için onay bekliyor
- Kontrol BAL önerisi
- İdrar kültürü: BÜ

3/6/2015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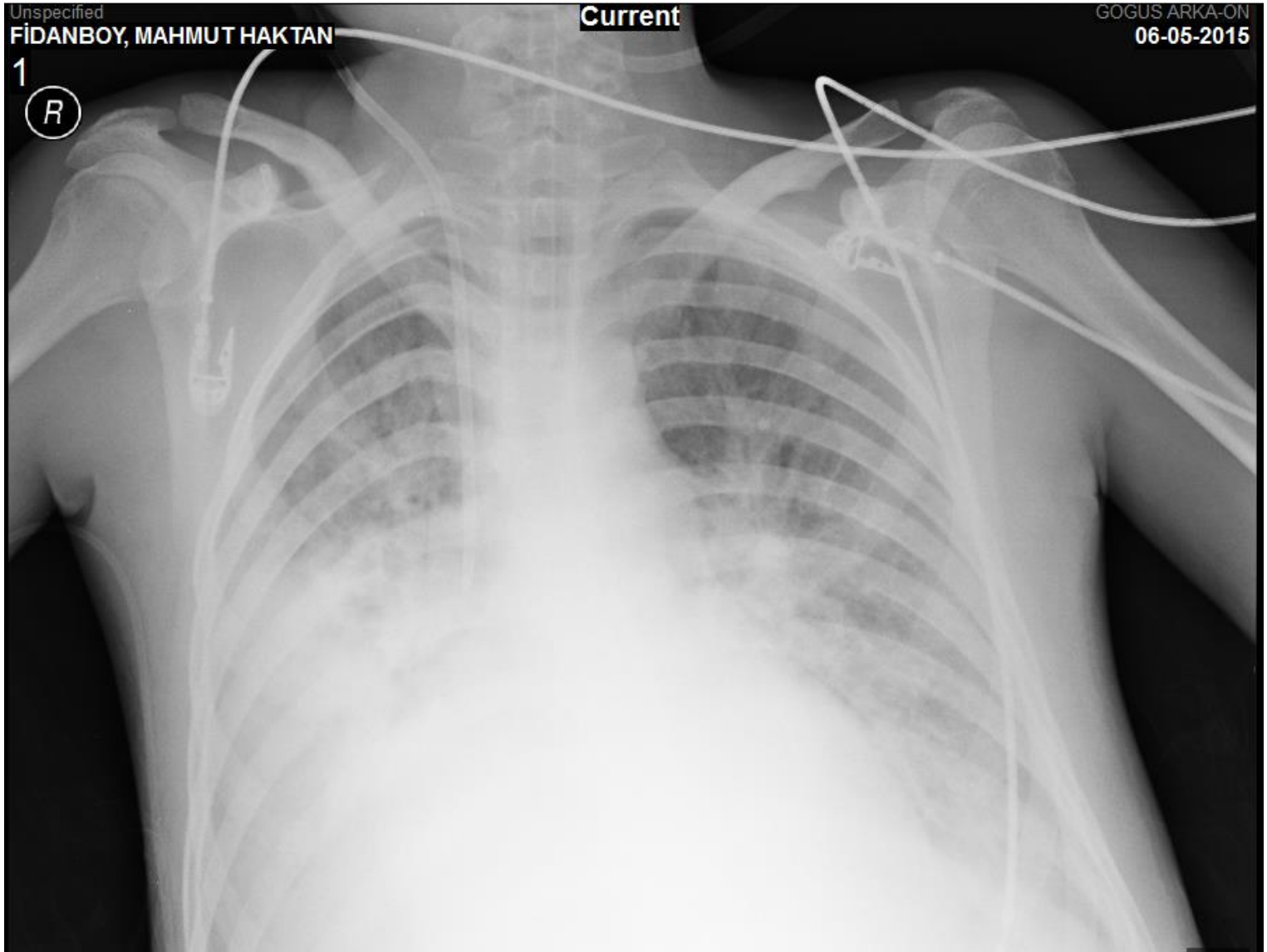
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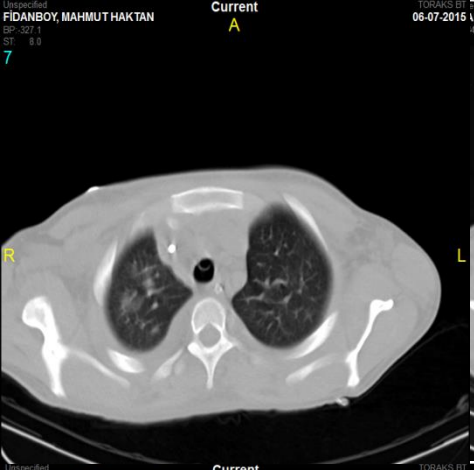
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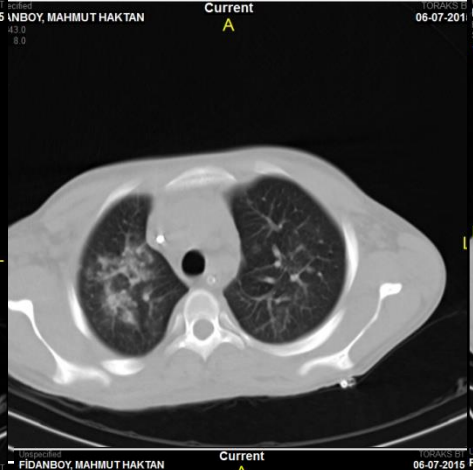
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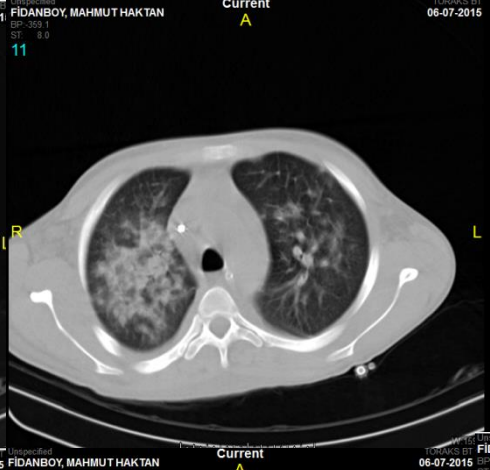
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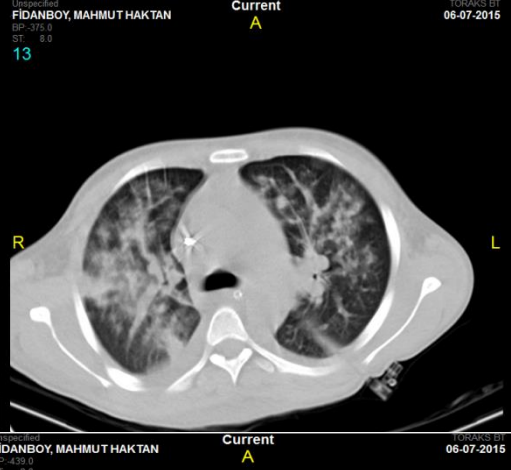
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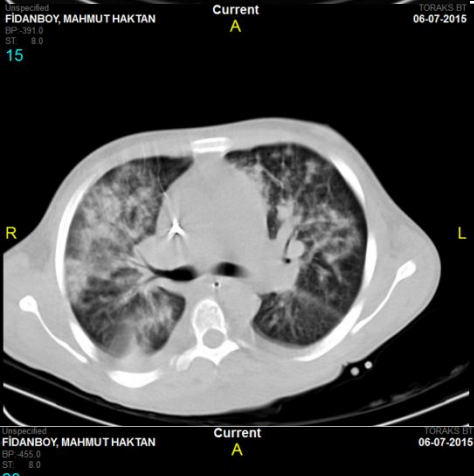
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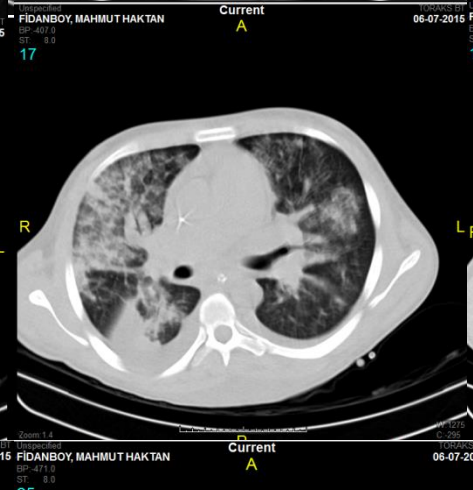
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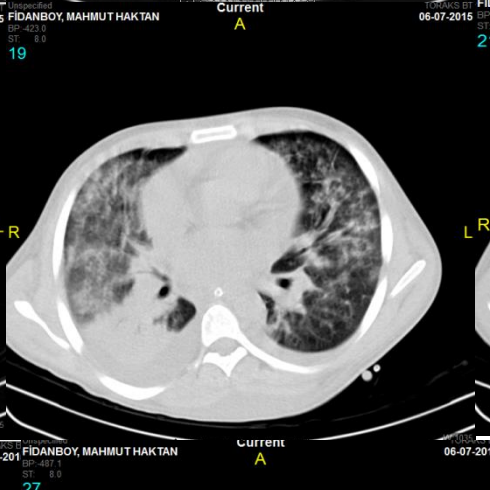
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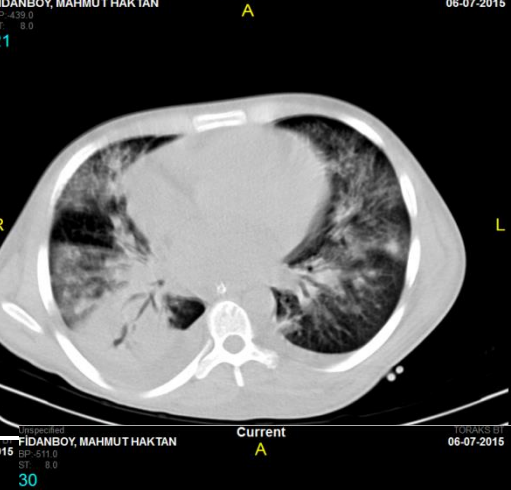
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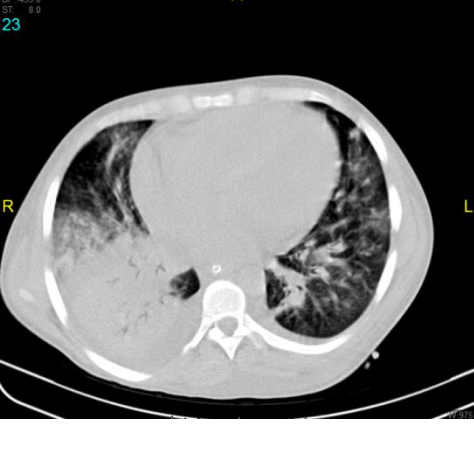
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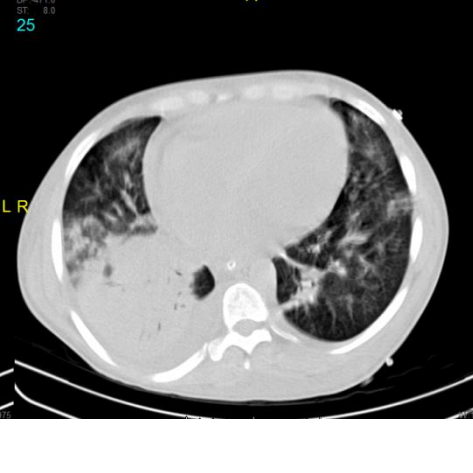
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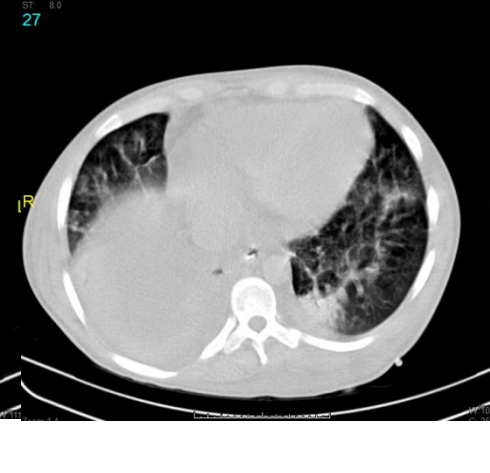
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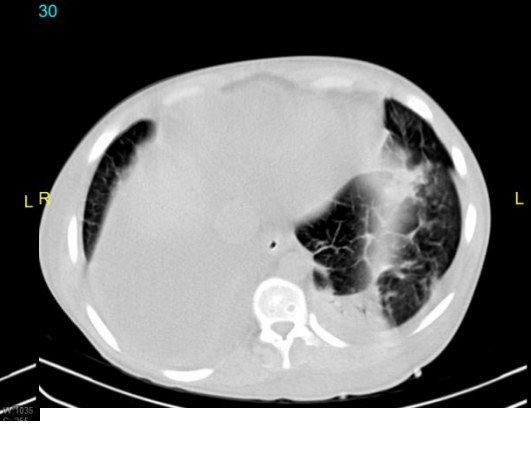
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06-07-2015
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7/6/2015 Toraks BT

1-Bilateral plevral efüzyon ve her iki akciğerlerdeki yaygın yoğunluk artışı pulmoner ödemi düşündürmektedir. Cilt altı yağ dokularındaki kirlenme ve cilt altı doku kalınlığındaki artış yaygın cilt altı ödemininin de bulunduğunu düşündürmüştür.

2-Sağ akciğer alt lob bazal segmentleri atelektaziktir. Süperior segment kısmen havalanmaktadır. Sol akciğer alt lobda küçük atelektazi alanları ve sekel parankimal değişiklikler bulunmaktadır.

3-Mediastende ve her iki aksillada büyüğünün kısa aksı 1cm olan lenf nodları izlenmiştir.

4-Kalp boyutu artmıştır. Ana pulmoner trunkus ve pulmoner arter çapları artmıştır.

- 8.Haziran.2015
- Ateş:39 ^{0}C
- MV desteğinde
- Femoralde SVK mevcut

- Kan gazlarında bozulma yok
- Solunum yolu sekresyonunda artış yok
- Kateter çıkış yeri temiz
- ETA, kan(2), kateterden kan ve idrar kültürü alındı
- BAL yapıldı
- YBÜ'de *A. baumannii* endemik, 2 hasta o dönemde VRE ile kolonize

- Lökosit:19500/mm^3, Trombosit:20000/mm^3
- Üre:112 mg/dl, Kreatinin:2.09 mg/dl
- CRP:5.7 mg/dl, PCT:46 ng/ml

- Hastada Sepsis, Ventilatörle İlişkili Pnömoni? düşünüldü

Hasta Adi	: **MAHMUT HAKTAN FİDANBOY**	Cinsiyet - Yaş	: (ERKEK) 19
Dosya No / Lab No .	: 01416166 / **9740248**	Bölüm	: Reanimasyon Yb.Kliniği.
Lab. Istem Tarihi	: 06/06/2015	Gönderen Dr.	: FERDA Ş. KAHVECİ
Lab. Kabul Tarihi	: 06/06/2015	Kurum	: TC.SGK.SSK GENEL MD.(1-DEVRI
Rapor Onay Tarihi	: 09/06/2015		
Gönderen Dr. Notu	:		

ÖRNEK GRUBU: ALT SOLUNUM YOLU ÖRNEKLERİ
ÖRNEK: ENDOTRAKEAL ASPİRAT (TAS)

İŞLEM : SOLUNUM SEKRESYONLARININ KANTİTATİF KÜLT **Işlem Tarihi : 06/06/2015**

SONUÇ : **Pozitif**

Üreyen Organizma : 1) KLEBSIELLA PNEUMONIAE SSP PNEUMONIAE

Yorum : **100.000 COL/ML UREDI E TEST ILE IMIPENEM..32..R MEROPENEM..32..R**

Direnç Profili :

Potential Carbapenemase Producer

Amikacin	>32	R	Ampicillin-Sulbactam	>16/8	R
Cefazolin	>8	R	Cefepime	>16	R
Cefoperazone-Sulbactam	>32/8	R	Cefoxitin	>16	R
Ceftriaxone	>4	R	Ciprofloxacin	>2	R
Ertapenem	>1	R	Gentamicin	>8	R
Imipenem	>8	R	Levofloxacin	>4	R
Meropenem	>8	R	Piperacillin-Tazobactam	>64/4	R
Ticarcillin-Clavulanate	>128/2	R	Tigecycline	>4	R
Trimethoprim-Sulfamethoxazole	>4/76	R			

Uludağ Üniversitesi
Uygulama ve Araştırma Merkezi

En olası enfeksiyon etkeni hangisi olabilir?

A-*Candida* spp.

B-*Klebsiella pneumoniae*

C-*Acinetobacter baumannii*

D-VRE

Kolonizasyonda Enfeksiyon Riski

- ÇM, Prospektif, 2 yıllık izlem, İtalya
- Rektal sürüntü pozitifliği olan hastalarda kan dolaşımı enfeksiyonu için risk faktörlerinin araştırılması
- 143 KDE ve 572 taşıyıcı
- Bağımsız risk faktörleri
  - -YBÜ'de yatmak
  - -Batına invazif girişim
  - -KT/RT
  - -Kolonize olan diğer bölgelerin sayısı

Giannella M et al. Clin Microbiol Infect 2014

Kolonizasyonda Enfeksiyon Riski

- 4 risk faktörünün en az ikisinin var olması
  - -Duyarlılık %93
  - -Özgüllük %42
  - -PPV %29
  - -NPV %93

Giannella M et al. Clin Microbiol Infect 2014

Ampirik tedavi nasıl olmalıdır?

- Kolistin
- Kolistin + Sulbaktam
- Kolistin + Meropenem
- Kolistin + Meropenem + Tigesiklin
- Kolistin + Daptomisin
- Meropenem uzamış infüzyon
- Ertapenem + Meropenem

Sürveyans Kültürleri

- ETA (haftada bir kez alındığında) kültürlerinin rehberlik ettiği başlangıç antibiyotik tedavisi %85 yeterli

  Jung B et al. Intensive Care Med 2009

- ETA(haftada iki kez alındığında) kültürlerinin rehberlik ettiği başlangıç antibiyotik tedavisi %95 yeterli

  Michel F et al. Chest 2005

- Tanıdan 1-3 gün önce alınan kültürlerle(ETA veya BAL), tanı sırasında alınan kültürler arasında benzerlik zayıf(0.63)

  Sanders KM et al. J Crit Care 2008

- 8.Haziran.2015
- Meropenem 2x1 g IV + Kolistin 2x150 mg IV
- SVK çekildi ve kültür için gönderildi
- 9.Haziran.2015 Kan kültürlerinde pozitif sinyal
- 10.Haziran.2015 ETA *A.baumannii*(Kol:S)

Kan Kültürü(2): *K. pneumoniae* Kolistin duyarlı

Hasta Adi	:	**MAHMUT HAKTAN FİDANBOY**	Cinsiyet - Yaş	:	(ERKEK) 19
Dosya No / Lab No .	:	01416166 / **9741483**	Bölüm	:	Reanimasyon Yb.Kliniği.
Lab. Istem Tarihi	:	08/06/2015	Gönderen Dr.	:	FERDA Ş. KAHVECİ
Lab. Kabul Tarihi	:	08/06/2015	Kurum	:	TC.SGK.SSK GENEL MD.(1-DEVRI
Rapor Onay Tarihi	:	11/06/2015			
Gönderen Dr. Notu	:				

ÖRNEK GRUBU: KAN
ÖRNEK: KAN (BACTEC) İLE
VÜCUT BÖLGESİ: KATETERDEN

İŞLEM : KAN KÜLTÜRÜ (BACTEC İLE) **İşlem Tarihi : 08/06/2015**

SONUÇ : **Pozitif**

Üreyen Organizma : 1) KLEBSIELLA PNEUMONIAE SSP PNEUMONIAE

Yorum : E TEST ILE MIK IMIPENEM..32..R
MEROPENEM..32..R

Direnç Profili :

Potential Carbapenemase Producer

Amikacin	>32	R	Ampicillin-Sulbactam	>16/8	R
Cefazolin	>8	R	Cefepime	>16	R
Cefoperazone-Sulbactam	>32/8	R	Cefoxitin	>16	R
Ceftriaxone	>4	R	Ciprofloxacin	>2	R
Ertapenem	>1	R	Gentamicin	>8	R
Imipenem	>8	R	Levofloxacin	>4	R
Meropenem	>8	R	Piperacillin-Tazobactam	>64/4	R
Ticarcillin-Clavulanate	>128/2	R	Tigecycline	4	I
Trimethoprim-Sulfamethoxazole	>4/76	R			

Uludağ Üniversitesi
Uygulama ve Araştırma Merkezi

Hasta Adi	:	**MAHMUT HAKTAN FİDANBOY**	Cinsiyet - Yaş	:	(ERKEK) 19
Dosya No / Lab No .	:	01416166 / **9741482**	Bölüm	:	Reanimasyon Yb.Kliniği.
Lab. Istem Tarihi	:	08/06/2015	Gönderen Dr.	:	FERDA Ş. KAHVECİ
Lab. Kabul Tarihi	:	09/06/2015	Kurum	:	TC.SGK.SSK GENEL MD.(1-DEVRI
Rapor Onay Tarihi	:	10/06/2015			
Gönderen Dr. Notu	:				

ÖRNEK GRUBU: ALT SOLUNUM YOLU ÖRNEKLERİ
ÖRNEK: ENDOTRAKEAL ASPİRAT (TAS)

İŞLEM : SOLUNUM SEKRESYONLARININ KANTİTATİF KÜLT **Işlem Tarihi** : 08/06/2015

SONUÇ : Pozitif

Üreyen Organizma : 1) ACINETOBACTER BAUMANNII/CALCOACETICUS COMPLEX Yorum : 100.000 COL/ML UREDI

Amikacin	>32	R	Ampicillin-Sulbactam	>16/8	R
Cefepime	>16	R	Cefoperazone-Sulbactam	>32/8	R
Ceftazidime	>16	R	Ciprofloxacin	>2	R
Colistin	<=1	S	Gentamicin	>8	R
Imipenem	>8	R	Levofloxacin	>4	R
Meropenem	>8	R	Piperacillin-Tazobactam	>64/4	R
Ticarcillin-Clavulanate	>128/2	R	Tigecycline	0	R
Trimethoprim-Sulfamethoxazole	>4/76	R			

Uludağ Üniversitesi
Uygulama ve Araştırma Merkezi

Hasta Adi	:	**MAHMUT HAKTAN FİDANBOY**	Cinsiyet - Yaş	:	(ERKEK) 19
Dosya No / Lab No .	:	01416166 / **9742120**	Bölüm	:	Reanimasyon Yb.Kliniği.
Lab. Istem Tarihi	:	08/06/2015	Gönderen Dr.	:	FERDA Ş. KAHVECİ
Lab. Kabul Tarihi	:	08/06/2015	Kurum	:	TC.SGK.SSK GENEL MD.(1-DEVRI
Rapor Onay Tarihi	:	08/06/2015			
Gönderen Dr. Notu	:				

ÖRNEK GRUBU: ALT SOLUNUM YOLU ÖRNEKLERİ
ÖRNEK: BRONKOALVEOLER LAVAJ (BAL)
VÜCUT BÖLGESİ: SAĞ

İŞLEM : SOLUNUM SEKRESYONLARININ KANTİTATİF KÜLT **İşlem Tarihi : 08/06/2015**

SONUÇ : **Pozitif**

Üreyen Organizma : 1) KLEBSIELLA PNEUMONIAE SSP PNEUMONIAE

Yorum : **E TEST ILE IMIPENEM..32..R**
MEROPENEM...32...R

Direnç Profili :

Potential Carbapenemase Producer

Amikacin	>32	R	Ampicillin-Sulbactam	>16/8	R
Cefazolin	>8	R	Cefepime	>16	R
Cefoperazone-Sulbactam	>32/8	R	Cefoxitin	>16	R
Ceftriaxone	>4	R	Ciprofloxacin	>2	R
Ertapenem	>1	R	Gentamicin	>8	R
Imipenem	>8	R	Levofloxacin	>4	R
Meropenem	>8	R	Piperacillin-Tazobactam	>64/4	R
Ticarcillin-Clavulanate	>128/2	R	Tigecycline	4	I
Trimethoprim-Sulfamethoxazole	>4/76	R			

Uludağ Üniversitesi
Uygulama ve Araştırma Merkezi

Karbapenem direnci hangi enzime bağlı olmayabilir?

A-NDM-1

B-VIM-1

C-OXA-48

D-KPC-2

E-NDM-1 ve OXA-48

Özgün Çalışma/Original Article *Mikrobiyol Bul 2016; 50(1): 21-33*

doi: 10.5578/mb.10695

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

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

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

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

KPC

- Temmuz 2014 – Aralık 2016
- 102 CR - *Klebsiella pneumoniae*

OXA-48	40
NDM	54
OXA-48 + NDM	6
KPC	2

Sağıroğlu P et al. Brazilian J Microbiol 2018

- Mart 2011-Mayıs 2012
- 24 CR-*Escherichia coli*

OXA-48	5
KPC-2	2

Kuşkucu MA et al. Travel Med Infect Dis 2016

Enzimin tahmini için başka hangi antibiyotik duyarlık sonucuna ihtiyaç var?

A-Seftazidim/Avibaktam

B-Aztreonam

C-Rifampisin

D-Fosfomisin

Aztreonam

- Metallo-beta laktamazlara dayanıklı
- *K. pneumoniae suşlarında* GSBL(TEM, SHV, CTX-M) mevcut

Klebsiella pneumoniae - Karbapenemaz(+)

- Metallo-beta-laktamaz(VIM, IMP)
- Oksasilinaz(OXA-48)
- KPC(1-7)
  -1996 yılında saptandı
  -Plazmid tarafından kodlanıyor
  -Tek başına direnç oluşturmaz, duyarlılığı azaltır
  -Direnç için dış membran permeabilitesinde azalma gerekir

Nordmann P et al. Lancet Infect Dis 2009

Table 1. Overview of Carbapenemase Enzyme Types in *Enterobacteriaceae*

Ambler Class (Active Site)	Example Enzymes	Host Organisms	Enzyme Substrates					Inhibition by Currently Available β-Lactamase Inhibitors (Clavulanic Acid, Tazobactam, and Sulbactam)	Region Mostly Found In
			Penicillins	Narrow Spectrum Cephalosporins	Extended Spectrum Cephalosporins	Aztreonam	Carbapenems		
A (serine)	KPC-2 to 22	Mainly found in *Klebsiella pneumoniae* (have been identified in other *Enterobacteriaceae* and nonfermenters)	Yes	Yes	Yes	Yes	Yes	Variable[a]	United States and worldwide
B (Zinc binding thiol –"MBLs")	NMD-1 IMP-I VIM-1	*Enterobacteriaceae* and nonfermenters	Yes	Yes	Yes	No	Yes	No	Southern Asia
D (serine)	OXA-48	*Enterobacteriaceae* (other types of OXA carbapenemases mainly found in *Acinetobacter* spp.)	Yes	Yes	Weak Activity[b]	No	Minimal Hydrolysis[b]	No	Southern Europe

Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

[a] Some KPC enzyme types, such as KPC-2, can hydrolyze clavulanic acid, tazobactam, and sulbactam. However, this ability to hydrolyze these β-Lactamase Inhibitors is uncommon in Class A enzymes [8, 9].

[b] OXA-48 is weakly active against extended spectrum cephalosporins and hydrolyzes carbapenems only minimally [10].

- Seftazidim/Avibaktam
  - -OXA ve KPC tarafından hidroliz edilmez
  - -MBL tarafından hidroliz edilir

- Aztreonam
  - -MBL ve OXA tarafından hidroliz edilmez
  - -KPC tarafından hidroliz edilir

Tedavi değişikliği yapar mısınız?

A-Evet

B-Hayır

Tedavi değişikliğini nasıl yaparsınız?

A-Mevcut tedaviye devam ederim

B-Tigesiklin eklerim

C-Kolistine devam ederim. Meropenemi uzamış infüzyon şeklinde veririm

D-Kolistini keserim. Meropenemi uzamış infüzyon şeklinde veririm

E-Tigesiklin + Meropenem + Amikasin veririm

F-Kolistini keserim. Meropenem + Ertapenem kombinasyonu veririm

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Continuous and Prolonged Intravenous β-Lactam Dosing: Implications for the Clinical Laboratory

Mordechai Grupper, Joseph L. Kuti, David P. Nicolau
Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut, USA

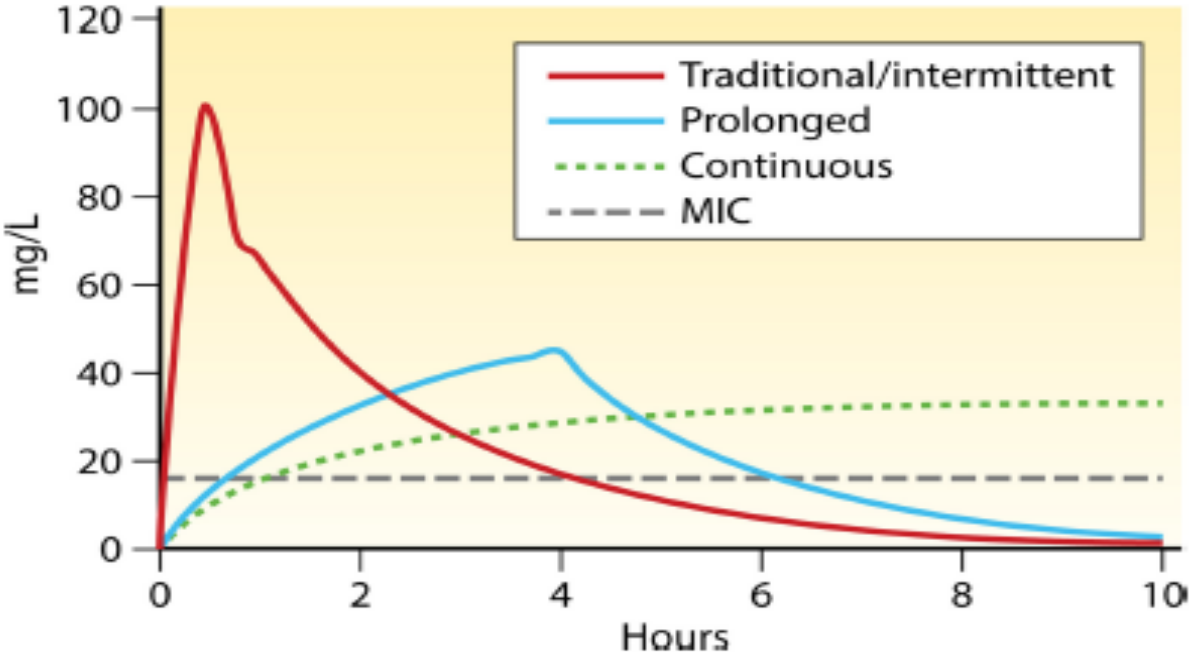

FIG 1 Schematic plot demonstrating the effects of prolonged and continuous beta-lactam infusion dosing regimens on the concentration-time curve and time above an MIC, compared with traditional intermittent infusion.

Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 10 October 2016, doi:10.4414/smw.2016.14368
Cite this as: Swiss Med Wkly. 2016;146:w14368

Prolonged administration of β-lactam antibiotics – a comprehensive review and critical appraisal

Michael Osthoff[a,b], Martin Siegemund[c], Gianmarco Balestra[d], Mohd H. Abdul-Aziz[e,f], Jason A. Roberts[f,g,h]

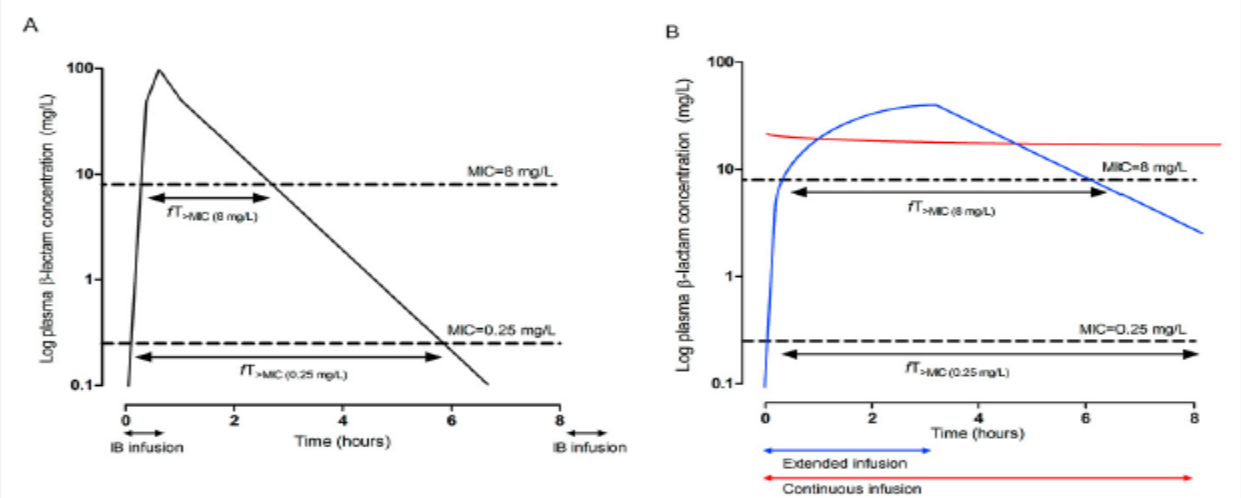

Figure 1

Differences in the time that β-lactam concentrations exceed the MIC ($fT_{>MIC}$) of two different pathogens (MIC of 0.125 mg/l and 8 mg/l, respectively) according to the mode of β-lactam administration. (A) Intermittent bolus administration. (B) Extended infusion (blue line) and continuous infusion (red line).
IB = intermittent bolus administration; MIC = minimal inhibitory concentration; $fT_{>MIC}$ = time that the free drug concentration is above the MIC

Uzamış İnfüzyon

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

Abdul-Aziz MH et al. J Antimicrob Chemother 2016

Meta-analiz

- 3 randomize çalışma
- 632 ağır sepsisli hasta
- Sürekli infüzyon alan hastalarda:
  - -Klinik iyileşme %55.4-%46.3,p=0.021
  - -Mortalite %19.6-%26.3, p=0.045

Roberts JA et al. Am J Respir Crit Care Med 2016

Tedavi Yaklaşımları

KPC(+) *K. pneumoniae* -Tedavi

- 41 bakteriyemi
- Ortanca yaş 62(25-90)
- KİKDE(%31.7), HKP(%24.4), ÜSE(%17.1)
- 28 günlük mortalite %39
- Kombinasyon tedavisi(kesin tedavi olarak) yaşamın devamı açısından bağımsız koruyucu faktör (OR, 0.07, p=0.02)

Qureshi Z et al. Antimicrob Agents Chemother 2010

KPC(+) *K. pneumoniae* -Tedavi

- Kombinasyon – mortalite 2/15(%13.3)
- Monoterapi – mortalite 11/19(%57.8), p=0.01

- En sık kombinasyon
  -Karbapenem + Kolistin
  -Karbapenem + Tigesiklin

Qureshi Z et al. Antimicrob Agents Chemother 2010

KPC(+) *K. pneumoniae* - Tedavi

- 2010-2011, ÇM(3), İtalya
- 125 Kan Dolaşımı Enfeksiyonu – KPC-Kp
- 30 günlük mortalite %41.6
- Monoterapide(tigesiklin, kolistin, gentamisin) mortalite %54.3
- Kombinasyonda(2 veya 3 AB) mortalite %34.1, p=0.02

Tumbarello M et al. Clin Infect Dis 2012

KPC(+) *K. pneumoniae* - Tedavi

- 2010-2013, ÇM(5), İtalya, KPC-Kp
- 447 Bakteriyemi
- 214 Bakteriyemi ile seyretmeyen enfeksiyon
- İn vitro etkili 2 ilaç kombinasyonu ile daha düşük mortalite(OR, 0.52)
- Meropenem MİK ≤ 8 mg/L ise, meropenem içeren kombinasyonlarda daha yüksek sağkalım

Tumbarello M et al. J Antimicrob Chemother 2015

KD-*K.pneumoniae*

- 2009-2010, ÇM(19), Yunanistan
- 127 hasta(39 KİKDE, 35 VİP)
- Kolistin direnci %20
- Tigesiklin direnci %33
- Gentamisin direnci %21
- Amikasin direnci %64
- 14. gün mortalitesi %23.5
- Klinik yanıtsızlık %45.2
- Kolistin alan hastalarda klinik yanıt daha iyi

Kontopidou F et al. Clin Microbiol Infect 2013

OXA-48(+) Enterobacteriaceae

- 36 Kan Dolaşımı Enfeksiyonu, KDE
- 26 *K.pneumoniae*
- 28.gün mortalitesi %50
- Kolistin içeren kombinasyonlarda mortalite daha az($p<0.001$)

Balkan İİ et al. Int J Infect Dis 2014

Klebsiella pneumoniae Bakteriyemisi

- Kartal Koşuyolu Hastanesi
- 2011-2017, retrospektif
- 210 Kp bakteriyemisi
- 111 Karbapenem dirençli
- 60 Kolistin dirençli(OXA-48 %78, NDM %35)
- 30.gün mortalitesi %58
- Mortalite için bağımsız risk faktörleri
  -Karbapenem direnci, APACHE II skoru yüksekliği
- Tedaviye amikasin eklenmesi koruyucu

Menekse S et al. Int J Infect Dis 2019

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

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

Findings Between Jan 1, 2004, and Dec 31, 2013, 480 patients with BSIs due to CPE were enrolled in the INCREMENT cohort, of whom we included 437 (91%) in this study. 343 (78%) patients received appropriate therapy compared with 94 (22%) who received inappropriate therapy. The most frequent organism was *Klebsiella pneumoniae* (375 [86%] of 437; 291 [85%] of 343 patients receiving appropriate therapy *vs* 84 [89%] of 94 receiving inappropriate therapy) and the most frequent carbapenemase was *K pneumoniae* carbapenemase (329 [75%]; 253 [74%] *vs* 76 [81%]). Appropriate therapy was associated with lower mortality than was inappropriate therapy (132 [38·5%] of 343 patients died *vs* 57 [60·6%] of 94; absolute difference 22·1% [95% CI 11·0–33·3]; adjusted hazard ratio [HR] 0·45 [95% CI 0·33–0·62]; p<0·0001). Among those receiving appropriate therapy, 135 (39%) received combination therapy and 208 (61%) received monotherapy. Overall mortality was not different between those receiving combination therapy or monotherapy (47 [35%] of 135 *vs* 85 [41%] of 208; adjusted HR 1·63 [95% CI 0·67–3·91]; p=0·28). However, combination therapy was associated with lower mortality than was monotherapy in the high-mortality-score stratum (30 [48%] of 63 *vs* 64 [62%] of 103; adjusted HR 0·56 [0·34–0·91]; p=0·02), but not in the low-mortality-score stratum (17 [24%] of 72 *vs* 21 [20%] of 105; adjusted odds ratio 1·21 [0·56–2·56]; p=0·62).

Interpretation Appropriate therapy was associated with a protective effect on mortality among patients with BSIs due to CPE. Combination therapy was associated with improved survival only in patients with a high mortality score. Patients with BSIs due to CPE should receive active therapy as soon as they are diagnosed, and monotherapy should be considered for those in the low-mortality-score stratum.

Yüksek mortalite skoru olan hastalarda kombinasyon tedavisi

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Combination Regimens for Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections

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Previous studies reported decreased mortality in patients with carbapenemase-producing *Klebsiella pneumoniae* bloodstream infections (BSIs) treated with combination therapy but included carbapenem-susceptible and -intermediate isolates, as per revised CLSI breakpoints. Here, we assessed outcomes in patients with BSIs caused by phenotypically carbapenem-resistant *K. pneumoniae* (CRKP) according to the number of *in vitro* active agents received and whether an extended-spectrum beta-lactam (BL) antibiotic, including meropenem, or an extended-spectrum cephalosporin was administered. We retrospectively reviewed CRKP BSIs at two New York City hospitals from 2006 to 2013, where all isolates had meropenem or imipenem MICs of ≥4 μg/ml. Univariate and multivariable models were created to identify factors associated with mortality. Of 141 CRKP BSI episodes, 23% were treated with a single active agent (SAA), 26% were treated with an SAA plus BL, 28% were treated with multiple active agents (MAA), and 23% were treated with MAA plus BL. Ninety percent of isolates had meropenem MICs of ≥16 μg/ml. Thirty-day mortality was 33% overall and did not significantly differ across the four treatment groups in a multivariable model ($P = 0.4$); mortality was significantly associated with a Pitt bacteremia score of ≥4 (odds ratio [OR], 7.7; 95% confidence interval [CI], 3.2 to 18.1; $P = 0.1$), and immunosuppression was protective (OR, 0.4; 95% CI, 0.2 to 1.0; $P = 0.04$). Individual treatment characteristics were also not significantly associated with outcome, including use of SAAs versus MAA (26% versus 38%, $P = 0.1$) or BL versus no BL (26% versus 39%, $P = 0.1$). In summary, in patients with CRKP BSIs caused by isolates with high carbapenem MICs, the role of combination therapy remains unclear, highlighting the need for prospective studies to identify optimal treatment regimens.

KDE – Polimiksin - Metaanaliz

- 19 kontrollu ve 6 tek kollu çalışma
- 1086 hasta
- Kontrollu çalışmalarda polimiksin ile tedavi edilen gruplarla kontrol grupları arasında mortalite, klinik yanıt ve mikrobiyolojik yanıt açısından fark yok

KDE – Polimiksin - Metaanaliz

- Alt grup analizinde polimiksin kombinasyonunda, polimiksin monoterapisine ve kontrol grubuna göre mortalite(28. veya 30.gün) düşük (OR, 0.36,p<0.01 ve OR,0.49,p<0.01)

Ni W et al. Braz J Infect Dis 2015

KDE – Kombinasyon - Metaanaliz

- 20 randomize olmayan çalışma
- 692 hasta
- Bakteriyemi, pnömoni, ÜSE
- Kombinasyon - Mortalite

-Tigesiklin + Gentamisin	%50
-Tigesiklin + Kolistin	%64
-Karbapenem + Kolistin	%67

KDE – Kombinasyon - Metaanaliz

- Monoterapi – Mortalite
  - -Kolistin %57
  - -Tigesiklin %80
- 194 Bakteriyemi
  - -Kombinasyonda mortalite daha az

Falagas ME et al. Antimicrob Agents Chemother 2014

Karbapenem Dirençli GNB

- Gözlemsel çalışmalarda polimiksin monoterapisinde mortalite yüksek
- *Klebsiella pneumoniae* bakteriyemilerinde bu fark daha belirgin
- Kanıt kalitesi?

Zusman O et al. J Antimicrob Chemother 2017

Kolistin ve MDR Gram Negatifler: Kombinasyon? Monoterapi?

- Gözlemsel çalışmalarda kombinasyon daha yüksek sağkalım ile birlikte
- RKÇ ise bu etki yok
- Mortalite oranlarında fark yok
- Asya'daki çalışmalarda *Acinetobacter* spp. bakteriyemilerinde yüksek doz kolistin ile kombinasyon etkili görünüyor

Vardakas KZ et al. Int J Antimicrob Agents 2018

Karbapenem Dirençli *Klebsiella pneumoniae*

- Çift Karbapenem Tedavisi
- Kolistin + Çift Karbapenem Tedavisi

KDKp
Ertapenem + Meropenem

- 2015 yılına kadar olgu sunumları
- 2015 yılından itibaren retrospektif olgu serileri
- Üriner sistem enfeksiyonları
- Karbapenemaz tipi(KPC)
- Kurtarma tedavisi
- Kolistine direnç varsa ya da kolistin nefrotoksisitesi
- Kolistin + çift karbapenem daha etkili

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Journal of Antimicrobial Chemotherapy

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

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Objectives: Antimicrobial therapy for sepsis caused by carbapenem- and colistin-resistant *Klebsiella pneumoniae* is not well established. We hypothesized that the early use of gentamicin in cases due to susceptible organisms would decrease the crude mortality rate of this infection.

Methods: This retrospective cohort study examined 50 cases of sepsis caused by carbapenem-resistant *K. pneumoniae* occurring between June 2012 and February 2013 during an outbreak of *K. pneumoniae* ST512 producing KPC-3, SHV-11 and TEM-1. Survival curves categorized by the use of gentamicin were constructed using the Kaplan–Meier method and compared using the log-rank test. Eight multivariate models using Cox regression were designed to study the risk factors for mortality and test the hypothesis.

Results: The 30 day crude mortality rate was 38%. The use of targeted gentamicin was associated with reduced mortality (20.7% versus 61.9%, $P=0.02$). In all multivariate regression models, the use of gentamicin was independently associated with lower mortality until Day 30 (HR 0.17–0.29, $P=0.03$–0.002 depending on the model) after controlling for other potential confounding variables such as age, optimal treatment, renal function, severity of infection, underlying disease, use of tigecycline and previous hospitalization.

Conclusions: Gentamicin reduced the mortality from sepsis caused by this *K. pneumoniae* ST512 clone producing KPC-3, SHV-11 and TEM-1.

Keywords: *K. pneumoniae*, carbapenem resistance, mortality

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

	Number (%) of patients (unless otherwise stated)				
	total ($n=50$)	no survivors ($n=19$)	survivors ($n=31$)	P	HR (95% CI)
Demographic variables					
age (years), median (range)	**60.5 (19–86)**	**67 (41–86)**	**55 (19–85)**	**0.046**	**1.03 (1.00–1.06)**
male	32 (64.0)	12 (63.2)	20 (64.5)	0.971	0.98 (0.38–2.49)
Comorbidities					
Charlson index, median (range)	4 (0–11)	4 (0–11)	3 (0–8)	0.178	1.13 (0.95–1.35)
renal failure[a]	**16 (32.0)**	**10 (52.6)**	**6 (19.4)**	**0.008**	**3.44 (1.39–8.54)**
Previous hospitalization (3 previous months)	**16 (32.0)**	**10 (52.6)**	**6 (19.4)**	**0.022**	**2.88 (1.16–7.14)**
Admission to the ICU	22 (44.0)	8 (42.1)	14 (45.2)	0.671	1.16 (0.59–2.59)
Invasive procedures (in previous week)					
mechanical ventilation	26 (52.0)	10 (52.6)	16 (51.6)	0.644	1.24 (0.49–3.16)
central venous catheter	36 (72.0)	11 (57.9)	25 (80.6)	0.349	0.62 (0.23–1.68)
urinary catheter	46 (92.0)	17 (89.5)	29 (93.5)	0.893	0.90 (0.21–3.92)
Prior antibiotic therapy (in the previous month)					
quinolones	**21 (42.0)**	**12 (63.2)**	**9 (29.0)**	**0.043**	**2.63 (1.03–6.71)**
amoxicillin/clavulanic acid	14 (28.0)	3 (15.8)	11 (35.5)	0.132	0.42 (0.12–1.43)
meropenem	23 (46.0)	9 (47.4)	14 (45.2)	0.764	1.14 (0.46–2.82)
cephalosporins	12 (24.0)	7 (36.8)	5 (16.1)	0.071	2.36 (0.93–6.02)
piperacillin/tazobactam	13 (26.0)	6 (31.6)	7 (22.6)	0.461	1.44 (0.55–3.79)
Type of infection					
pneumonia	24 (48.0)	8 (42.1)	16 (51.6)	0.356	1.07 (0.93–1.23)
purulent tracheobronchitis	4 (8.0)	1 (5.3)	3 (9.7)		
urinary tract infection	10 (20.0)	5 (26.3)	5 (16.1)		
surgical wound infection	4 (8.0)	1 (5.3)	3 (9.7)		
intra-abdominal infection	1 (2.0)	1 (5.3)	0 (0)		
infection of skin and soft tissue	1 (2.0)	0 (0)	1 (3.2)		
endocarditis	1 (2.0)	1 (5.3)	0		
primary or catheter-related bacteraemia	4 (8.0)	2 (10.5)	2 (6.5)		
infection of the CNS	1 (2.0)	0	1 (3.2)		
Bacteraemia	18 (36.0)	7 (36.8)	11 (35.5)	0.866	1.08 (0.43–2.57)
Severe sepsis/septic shock	**30 (60.0)**	**18 (94.7)**	**12 (38.7)**	**0.006**	**16.6 (2.21–125.1)**
CL_{CR} at start of antibiotic treatment (mL/min), mean ± SD	**96.2 ± 53.2**	**69.4 ± 38.0**	**112.6 ± 55.0**	**0.005**	**0.98 (0.97–0.99)**

Active empirical treatment	6 (12.0)	2 (10.5)	4 (12.9)	0.857	0.87 (0.20–3.78)
Time to initiation of optimal targeted treatment (days), mean (range)	2.1 (0–5)	1.7 (0–5)	2.2 (0–5)	0.405	0.86 (0.61–1.22)
Optimal targeted treatment	**37 (74.0)**	**9 (47.4)**	**28 (90.3)**	**0.001**	**0.18 (0.07–0.45)**
monotherapy	16 (32.0)	4 (21.1)	12 (38.7)	0.258	0.53(0.18–1.60)
tigecycline	8 (16.0)	3 (15.8)	5 (16.1)		
gentamicin	8 (16.0)	1 (5.3)	7 (22.6)		
combination therapy	21 (42.0)	5 (26.3)	16 (51.6)	0.058	0.37 (0.13–1.03)
tigecycline + gentamicin	21 (42.0)	5 (26.3)	16 (51.6)		
Optimal targeted treatment with tigecycline	29 (58.0)	8 (42.1)	21 (67.7)	0.059	0.41 (0.16–1.03)
Optimal targeted treatment with high-dose tigecycline	10 (20.0)	1 (5.3)	9 (29.0)	0.098	0.18 (0.20–1.37)

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

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

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

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

Abstract: Carbapenem-resistant *Enterobacteriaceae* (CRE) infections are prevalent worldwide; they have few effective treatments and this jeopardizes public health. Clinicians often use tigecycline to combat CRE, but its clinical efficacy remains controversial. Therefore, to compare the efficacy and safety of tigecycline in treating CRE infections compared with that of other antimicrobial agents, and to evaluate whether combination therapy and high-dose regimens are beneficial, we performed a systematic review and meta-analysis.

PubMed and Embase were searched for controlled trials or cohort studies reporting the efficacy and/or safety of tigecycline-based regimens to treat CRE infections. Statistical analyses were performed using the Comprehensive Meta-Analysis V2.2. All meta-analyses were performed based on fixed- or random-effects model, and the I^2 method was used to assess heterogeneity.

Twenty-one controlled studies and 5 single-arm studies were included in this systematic review. With regard to the controlled studies, the tigecycline groups did not differ significantly from the control groups in terms of overall mortality (Odds ratio (OR) = 0.96 [95% confidence interval (CI) = 0.75–1.22; $P = 0.73$]), clinical response rate (OR = 0.58 [95% CI = 0.31–1.09; $P = 0.09$]), or microbiological response rate (OR = 0.46 [95% CI = 0.15–1.44; $P = 0.18$]). Subgroup analyses showed that 30-day mortality was significantly lower in patients who received tigecycline combination therapy than in those who received monotherapy (OR = 1.83 [95% CI = 1.07–3.12; $P = 0.03$]) and other antibiotic regimens (OR = 0.59 [95% CI = 0.39–0.88; $P = 0.01$]), respectively. In addition, high-dose tigecycline regimens differed significantly from standard dose schedules in terms of ICU mortality (OR = 12.48 [95% CI = 2.06–75.43; $P = 0.006$]). The results of the 5 single-arm studies corroborated the findings of the controlled studies.

Our results indicated that the efficacy of tigecycline in treating CRE infections is similar to that of other antibiotics. Tigecycline combination therapy and high-dose regimens may be more effective than monotherapy and standard-dose regimens, respectively. Nonetheless, considering that the current available evidence is limited, well-designed randomized controlled trials are urgently needed to clarify the comparative efficacy of tigecycline in treating CRE infections.

(*Medicine* 95(11):e3126)

Abbreviations: CI = confidence interval, CRE = carbapenem-resistant *Enterobacteriaceae*, ICU = intensive care unit, NOS = Newcastle–Ottawa scale, OR = odds ratio, RCT = randomized controlled trial.

INTRODUCTION

Enterobacteriaceae, such as *Klebsiella pneumoniae, Escherichia coli*, and *Enterobacter cloacae*, are frequently involved in hospital-associated infections. In particular, strains that produce extended-spectrum β-lactamases are common.[1] Carbapenems are the most broadly used first-line antibiotics for such infections. However, widespread use of these drugs has resulted in the emergence of carbapenem-resistant strains, most of which produce carbapenemases and are, therefore, resistant to the drug.[2] In recent years, these versatile carbapenemases have spread worldwide among the *Enterobacteriaceae*, especially *K pneumoniae*. For this reason, nosocomial outbreaks of carbapenem-resistant *Enterobacteriaceae* (CRE) are frequent worldwide, leading to prolonged hospital stays and higher mortality rates.[3]

NDM-1(+) KDKp

- Kolistin + Fosfomisin çok nadir olarak sinerjik
- Kolistin + Tigesiklin çok nadir olarak sinerjik

Berçot B et al. J Antimicrob Chemother 2011

Tigesiklin + Kolistin

- OXA-48(+) Kp: Sinerjik
- KPC-3(+) Kp: İntermediate veya Aditif
- VIM-1 ve KPC-2(+) Kp: İntermediate veya Aditif

Betts JW et al. Antimicrob Agents Chemother 2014

CURRENT OPINION

The management of multidrug-resistant *Enterobacteriaceae*

Matteo Bassetti, Maddalena Peghin, and Davide Pecori

Curr Opin Infect Dis 2016, 29:583–594

Table 5. Expert opinion treatment options for *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*. Dose adjustment is recommended depending on renal function and antimicrobial susceptibility tests[a]

KPC-Kp meropenem MIC ≤ 8–16 mg/l			
Primary BSIs	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Meropenem 2 g q 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycin 4 g every 4 h i.v.	Inhaled antibiotics[b] + meropenem 2 g q 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycine 4 g every 4 h i.v.	Meropenem 2 g q 8 h i.v. (f) + tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) or gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or fosfomycin 4 g every 4 h i.v.	Meropenem 2 g q 8 h i.v. (f) + fosfomycin 4 g every 4 h i.v. + gentamicin 3–5 mg/kg/day every 24 h i.v. (i) or colistin 4.5 MU every 12 h i.v. (h)
Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.

KPC-Kp meropenem MIC > 8–16 mg/l			
Primary BSIs	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Tigecycline 100 mg every 12 h .i.v (g) + colistin 4.5 MU every 12 h i.v. (h) + fosfomycin 4 g every 4 h i.v. or gentamicin 3–5 mg/kg/ every 24 h i.v. (i)	Inhaled antibiotics[b] + colistin 4.5 MU every 12 h i.v. (h) + tigecycline 100 mg every 12 h i.v. (g) or gentamicin 3 mg/kg/day every 24 h i.v. (i) +/− rifampin 600–900 mg every 24 h i.v.	Tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) + gentamicin 3–5 mg/kg/day every 24 (i)	Colistin 4.5 MU every 12 h i.v. (i) + fosfomycin 4 g every 6 h i.v. +/− trimethoprim–sulfamethoxazole 20 mg/kg/day (m)
Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v. + metronidazole i.v.	Ceftazidime–avibactam 2.5 g every 8 h i.v.
KPC-Kp meropenem MIC > 8–16 mg/l Colistin-R			
Primary BSIs	**Pneumonia**	**Abdominal infection**	**Urinary tract infection**
Tigecycline 100 mg every 12 h i.v. (g) + colistin 4.5 MU every 12 h i.v. (h) + rifampin 600–900 mg every 24 h i.v.	As for BSIs + inhaled antibiotics[b]	As for BSIs	As for BSIs
Ertapenem 500 mg every 6 h i.v. (c) + meropenem 2 g q 8 h i.v. (f)			
Ertapenem 500 mg every 6 h i.v. (c) + doripenem 500 mg every 8 h (l)			
Ceftazidime-avibactam 2.5 g every 8 h i.v.			

(c) Ertapenem: maintenance dose with continuous infusion (500 mg every 6 h in 4 h).
(f) Meropenem: loading dose (2 g in 1 h) followed by maintenance doses with continuous infusion (2 g every 8 h in 6 h).
(g) Tigecycline: loading dose (200 mg) followed by maintenance doses with 100 mg every 12 h.
(h) Colistin: loading dose (9 MU) followed by maintenance doses with 4.5 MU every 12 h.
(i) Gentamicin once a day or amikacin 15–20 mg/kg/day every 24 h i.v.
(l) Doripenem: maintenance doses with doripenem 500 mg every 8 h (infusion in 1 h).
(m) Trimethoprim–sulfamethoxazole divided every 6 h.
BSI, bloodstream infection; i.v., intravenous; KPC-Kp, *Klebsiella pneumoniae* carbapenemase *Klebsiella pneumoniae*; MIC, minimum inhibitory concentration; MU, million units.
[a]Antimicrobial susceptibility test. Colistin: MIC 2 mg/l or less, continue colistin; MIC more than 2 mg/l, consider alternative in-vitro active antimicrobial. Tigecycline: MIC 1 mg/l or less, consider tigecycline; MIC more than 1 mg/l, consider alternative in-vitro active antimicrobial. Fosfomycin: MIC 32 mg/l or less, consider fosfomycin; MIC more than 32 mg/l, consider alternative in-vitro active antimicrobial. Aminoglycoside: MIC 2 mg/l or less for gentamicin/tobramycin or 4 mg/l or less for amikacin, consider aminoglycoside; MIC more than 2 for gentamicin/tobramycin or more than 4 mg/l for amikacin, consider alternative in-vitro active antimicrobial.
[b]Inhaled antibiotic: colistin 2 MU every 8 h or tobramycin 300 mg every 12 h or amkacin 250 mg every 24 h.

Karbapenem Dirençli Kp - Meropenem MİK

- Yüksek doz meropenem ile yüksek MİK (≥16 mg/L)'de bile fayda mevcut

  Giannella M et al. Int J Antimicrob Agents 2018

- Meropenem yüksek doz ve uzamış infüzyon ile MİK 32-64 mg/l'de terapötik konsantrasyonlara ulaşabilir

  Giacobbe DR et al. Eur J Clin Microbiol Infect Dis 2017

- Meropenem MİK≤16 mg/L'de kolistin ile bakterisidal

  Sharma R et al. Int J Antimicrob Agents 2017

CURRENT OPINION

Optimizing therapy in carbapenem-resistant *Enterobacteriaceae* infections

Mario Tumbarello[a], *Angela Raffaella Losito*[b], *and Helen Giamarellou*[c]

Table 3. Antimicrobial regimens currently recommended for infections caused by carbapenem-resistant *Enterobacteriaceae*

Drug	Dose	Comments
Colistin	Loading dose 9 million IU IV, then 4.5 million IU IV q12h Loading dose 5 mg/kg IV, then 2.5 mg/kg IV q12h	Dosage for severe infections. Dose adjustment needed for renal failure
Polymyxin B	Loading dose 2.5 mg/kg IV (2-h infusion), then; 1.5 mg/kg q12h (1-h infusion)	No dose adjustment required for renal impairment
Tigecycline	Loading dose 100–200 mg IV, then 50–100 mg IV q12h	Higher doses required for severe infections. Avoid in UTIs (urinary concentrations inadequate)
Gentamicin	5–7 mg/kg IV q24h (1-h infusion)	TDM recommended
Amikacin	15–30 mg/kg IV q24h (1-h infusion)	TDM recommended
Fosfomycin	6–8 g IV q8h	Use with other active drugs; may cause elevated serum sodium levels
Meropenem	2 g IV q8h (extended infusion)	Use with active drugs only for CRE isolates with meropenem MICs $\leq$8
Ceftazidime–avibactam	2.5 g (2 g/500 mg) IV q8h	Active against KPC and OXA-48 producers; inactive against MBL producers; First-line therapy for high-risk patients with CRE infections caused by susceptible strains.
Meropenem–vaborbactam	4 g (2g/2g) IV q8h	Active against: KPC producers; Inactive against: OXA 48 and MBL producers; Approved 2017 by FDA for cUTI caused by susceptible gram-negative bacilli.

cUTI, complicated urinary tract infection; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

Tedavi değişikliğini nasıl yaparsınız?

A-Mevcut tedaviye devam ederim

B-Tigesiklin eklerim

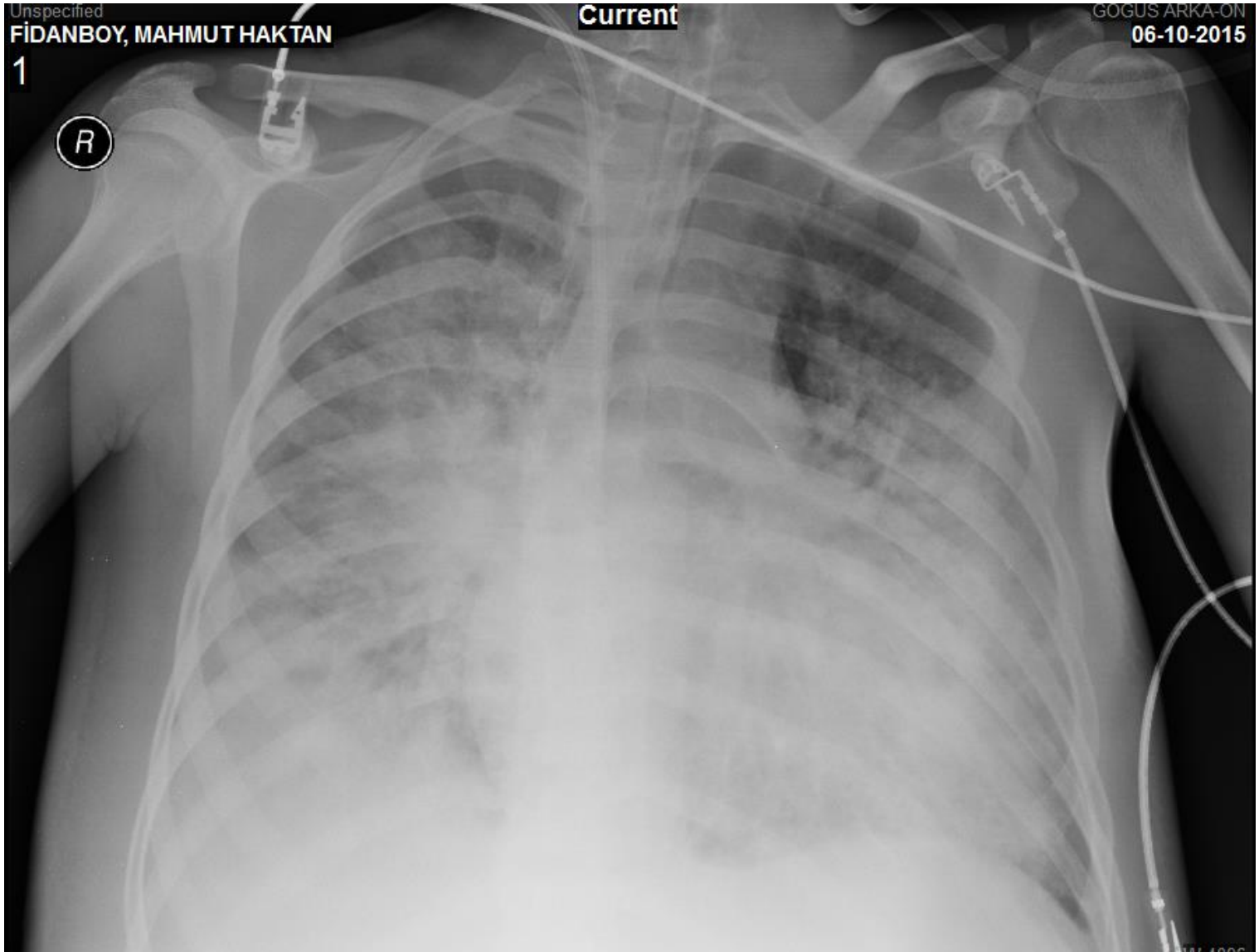
C-Kolistine devam ederim. Meropenemi uzamış infüzyon şeklinde veririm

D-Kolistini keserim. Meropenemi uzamış infüzyon şeklinde veririm

E-Tigesiklin + Meropenem + Amikasin veririm

F-Kolistini keserim. Meropenem + Ertapenem kombinasyonu veririm

10/6/2015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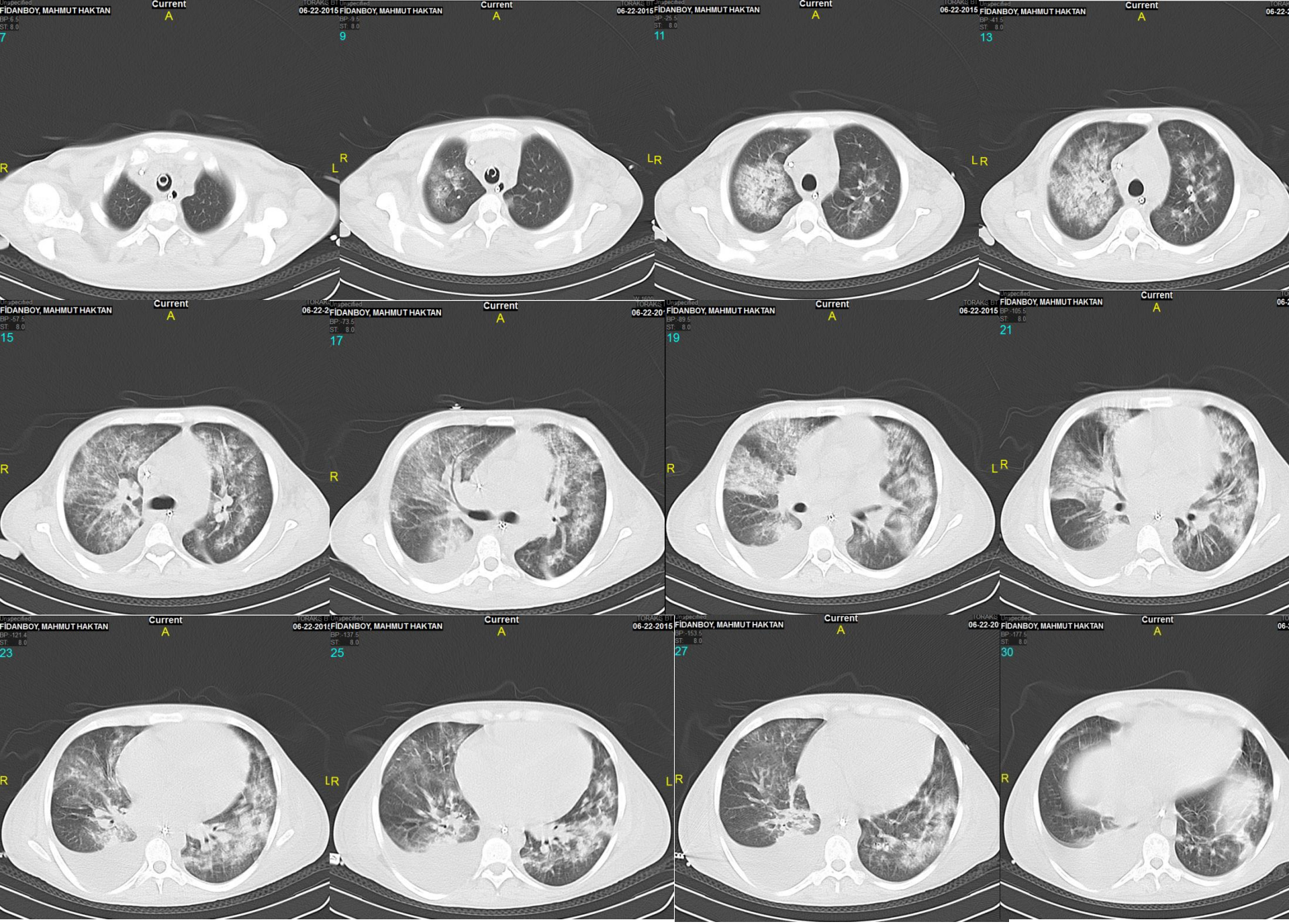
- Şuur açık
- Entübe ve MV desteğinde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22/6/2015 Toraks BT

- 1.Her iki akciğerde izlenen periferik akciğerin kısmen korunduğu keskin sınırlı birleşmeye meyilli irregüler yoğunluk artımları plevral sıvı ve cilt altı dokulardaki dansite artışı ile birlikte değerlendirildiğinde pulmoner ödem lehine değerlendirilmektedir. Ancak süperimpoze enfeksiyon varlığı da söz konusu olabilir. Bu görünümlerde bir önceki incelemeye göre belirginleşme mevcuttur. Ancak sağ akciğer alt lobdaki atalektazi/konsolidasyon görünümü ise belirgin gerilemiştir.
- 2.Kalp boyutu ve pulmoner arter çaplarında artış izlenmiştir. Mediastendeki lenf nodlarında belirgin farklılık izlenmemiştir. Lenf nodları pulmoner ödem ve enfeksiyona bağlı olabilir.

- Kolistin + Meropenem tedavisi 14 güne tamamlandı
- 7.Temmuz.2015 Kadavradan karaciğer transplantasyonu
- 11.Kasım.2015 Muhtemelen Kalp Yetmezliğinden Eksitus(EF %25)

Aşağıdakilerden hangisi tedavide yeni seçenek olabilir?

A-Plazomisin

B-Eravasiklin

C-Seftazidim/Avibaktam

D-Seftarolin/Avibaktam

E-Fosfomisin

F-İmipenem/Relebaktam

G-Meropenem/Vaborbaktam

Tedavide Yeni Seçenekler

-Seftazidim/Avibaktam

-Seftarolin/Avibaktam

-Plazomisin

-Eravasiklin

-İmipenem/Relebaktam

-Meropenem/Vaborbaktam

-Aztreonam/Avibaktam

-Seftolozan/Tazobaktam

-Sefiderokol

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

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

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

The management of multidrug-resistant *Enterobacteriaceae*

Matteo Bassetti, Maddalena Peghin, and Davide Pecori

Table 6. Drugs recently approved by Food and Drug Administration or in clinical development with activity against multidrug-resistant *Enterobacteriaceae*

Drug name	Development phase	Company	Spectrum	Potential indications
Cephalosporin				
S-649266	Phase 2	Shionogi, Inc.	Activity against KPC and NDM-1	Complicated urinary tract infections
Cephalosporin + β-lactamase inhibitor				
Ceftolozane–tazobactam	Approved by FDA in December 2014	Cubist Pharmaceuticals/Merck	Activity against ESBLs	Complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis
Ceftazidime–avibactam	Approved by FDA in February 2015	Actavis/AstraZeneca	Activity against KPCs and OXA-48 (not active against MBLs)	Complicated intra-abdominal infections (in combination with metronidazole), complicated urinary tract infections including pyelonephritis, hospital-acquired bacterial pneumonia
Ceftaroline fosamil–avibactam	Entering Phase 3	Actavis/AstraZeneca	Activity against KPCs and OXA-48 (not active against MBLs)	Complicated urinary tract infections
Monobactam + novel β-lactamase inhibitor				
Aztreonam–avibactam	Phase 2	Actavis/AstraZeneca	Activity against MBLs such as NDM	Complicated bacterial Infections
Carbapenem + novel β-lactamase inhibitor				
Meropenem–RPX7009	Phase 3	Rempex Pharmaceuticals	Activity against KPCs	Complicated urinary tract infections, hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, bloodstream infections
Imipenem/cilastatin–relebactam	Phase 3	Merck Sharp & Dohme Corp.	Activity against class A and C β-lactamases	Complicated urinary tract infections, including pyelonephritis, hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia
Aminoglycoside				
Plazomicin	Phase 3	Achaogen	Active against most KPCs (not active against many NDMs)	Complicated urinary tract infections, hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, bloodstream infections
Tetracycline				
Eravacycline	Phase 3	Tetraphase Pharmaceuticals	Active against KPCs	Complicated urinary tract infections and complicated intra-abdominal infections

ESBL, extended-spectrum β-lactamases; FDA, Food and Drug Administration; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase.

Seftazidim/Avibaktam

- Avibaktam: Beta-laktam olmayan bir beta-laktamaz inhibitörü
- KPC ve OXA-48 enzimlerine etkili
- MBL enzimine etkisiz

- Komplike İntra Abdominal Enfeksiyon
- Komplike ÜSE
- FDA ve EMA onaylı

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

Avibaktam

- OXA-48(+) *K. pneumoniae*
- İmipenem dirençli
- İmipenem + Avibaktam(S)
- Sefepim + Avibaktam(S)
- Seftazidim + Avibaktam(S)

Aktaş Z et al. Int J Antimicrob Agents 2012

Clinical Infectious Diseases

MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

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Background. The efficacy of ceftazidime-avibactam—a cephalosporin–β-lactamase inhibitor combination with in vitro activity against *Klebsiella pneumoniae* carbapenemase–producing carbapenem-resistant Enterobacteriaceae (CRE)—compared with colistin remains unknown.

Methods. Patients initially treated with either ceftazidime-avibactam or colistin for CRE infections were selected from the Consortium on Resistance Against Carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE), a prospective, multicenter, observational study. Efficacy, safety, and benefit-risk analyses were performed using intent-to-treat analyses with partial credit and the desirability of outcome ranking approaches. The ordinal efficacy outcome was based on disposition at day 30 after starting treatment (home vs not home but not observed to die in the hospital vs hospital death). All analyses were adjusted for confounding using inverse probability of treatment weighting (IPTW).

Results. Thirty-eight patients were treated first with ceftazidime-avibactam and 99 with colistin. Most patients received additional anti-CRE agents as part of their treatment. Bloodstream (n = 63; 46%) and respiratory (n = 30; 22%) infections were most common. In patients treated with ceftazidime-avibactam versus colistin, IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was 9% versus 32%, respectively (difference, 23%; 95% bootstrap confidence interval, 9%–35%; $P = .001$). In an analysis of disposition at 30 days, patients treated with ceftazidime-avibactam, compared with those treated within colistin, had an IPTW-adjusted probability of a better outcome of 64% (95% confidence interval, 57%-71%). Partial credit analyses indicated uniform superiority of ceftazidime-avibactam to colistin.

Conclusions. Ceftazidime-avibactam may be a reasonable alternative to colistin in the treatment of *K. pneumoniae* carbapenemase–producing CRE infections. These findings require confirmation in a randomized controlled trial.

Keywords. carbapenem-resistant Enterobacteriaceae; *Klebsiella pneumoniae*; colistin; ceftazidime-avibactam; benefit-risk.

Short Communication

Clinical characteristics and prognosis of infections caused by *OXA-48* carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam

Cristina De la Calle[a,*], Olga Rodríguez[a], Laura Morata[a], Francesc Marco[b], Celia Cardozo[a], Carolina García-Vidal[c], Ana Del Río[a], Csaba Feher[a], Martina Pellicé[a], Pedro Puerta-Alcalde[a], Josep Mensa[a], Alex Soriano[c], Jose Antonio Martínez[c]

Background: Ceftazidime-avibactam has in vitro activity against Gram-negative bacilli that produce Class A, C and some D β-lactamases, and has been successfully used in the treatment of infections caused by cephalosporin and carbapenem-resistant Enterobacteriaceae. However, actual experience in the treatment of *OXA-48* carbapenemase-producing Enterobacteriaceae (CPE) is limited.

Objective: To review the characteristics and prognosis of *OXA-48* CPE infections treated with ceftazidime-avibactam since introduction of the drug to the current centre during the period October 2014 to December 2016.

Methods: Retrospective assessment of episodes of infection caused by *OXA-48* CPE treated with ceftazidime-avibactam, analysing data collected from infection diagnosis until 90 days after the end of treatment.

Results: Twenty-four episodes were analysed. Ceftazidime-avibactam was given as the initial definitive treatment in 15 (62.5%) and as salvage therapy in nine (37.5%). Intraabdominal (seven, 29%), urinary (six, 25%) and respiratory (five, 21%) were the most common sources. The 30-day and 90-day mortality rates were 8.3% and 20.8%, respectively. Clinical cure at 30 days was achieved in 62.5% of episodes. Four (16.7%) patients had adverse events, two of them were related to impaired renal function. Among patients who finished the treatment with ceftazidime-avibactam, seven (35%) were diagnosed with infection recurrence within 90 days of the end of treatment.

Conclusions: From experience, ceftazidime-avibactam is an effective drug for treating infections due to *OXA-48* CPE. From these results a better safety profile than the current best available therapy could be expected.

Seftolozan/Tazobaktam

- *P aeruginosa*'ya etkili
- ESBL(+)'lere etkili
- k-ÜSE
- k-İAE
- Nozokomiyal pnömoni

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017
Kollef MH et al. Lancet Infect Dis 2019

Aztreonam/Avibaktam

- Aztreonam: ESBL ve KPC tarafından hidroliz edilir
- ESBL, MBL ve KPC'ye etkili
- *A baumannii*'ye etkisiz
- Aztreonam MİK(32-64)-P *aeruginosa*'ya az etkili

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

İmipenem/Silastatin/Relebaktam

- Relebaktam: Beta-laktam olmayan bir serin beta-laktamaz inhibitörü
- KPC'ye etkili
- OXA-48 Kp ve OXA-23 Ab 'ye etkisiz
- Faz 2: k-İAE ve k-ÜSE
- Faz 3: HGP(Pip/Tazo) ve İmipenem-R GNB(İmipenem/silastatin + Kolistin)

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

Meropenem/Vaborbaktam

- Vaborbaktam: Boronik asit inhibitörü
- KPC(+) Kp'ye etkili
- OXA(+) Ab'ye az etkili

- Faz 3: k-ÜSE(Pip/tazo'dan üstün) ve KDE(k-ÜSE, HGP ve Bakteriyemi) enfeksiyonlarında etkili

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

Plazomisin

- Sisomisin derivesi
- KDE'lere etkili
- NDM(+)'lere etkisiz
- OXA(+) Ab'ye etkili
- Non-fermentatiflere az etkili

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

Eravasiklin

- Sentetik fluorosiklin tetrasiklin
- KPC(+), OXA(+), NDM(+) Enterobacteriaceae'ya etkili
- Etkinlik tigesikline benzer
- *Burkholderia* spp. ve *P aeruginosa*'ya etkisiz

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

Sefiderokol

- Siderofor sefalosporin
- Katekol yan zinciri ile demir iyonu bağlar
- Sefiderokol ve demir iyon kompleksi ile bakteriye transfer olur ve hücre duvarını hasara uğratır
- KDE, MDR *P aeruginosa* ve *A baumannii*'ye etkili
- Karbapenemazlara dayanıklı
- KDE için çalışmalar devam ediyor

Thaden JT et al. Virulence 2016
Wright H et al. Clin Microbiol Infect 2017

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New Treatment Options against Carbapenem-Resistant *Acinetobacter baumannii* Infections

Burcu Isler,[a] Yohei Doi,[b] Robert A. Bonomo,[c,d] David L. Paterson[e]

TABLE 1 New therapeutic options

Drug	Preclinical	Phase I	Phase II	Phase III	FDA approved
Siderophore cephalosporins					
Cefiderocol	✓	✓	✓	✓	-
Others					
GSK-3342830	✓	-[a]	-	-	-
Fimsbactin plus daptomycin	✓	-	-	-	-
GT-1	✓	-	-	-	-
Tetracyclines					
Eravacycline	✓	✓	✓	✓	✓
TP-6076	✓	✓	-	-	-
New non-β-lactam–β-lactamase inhibitors paired with existing β-lactam antibiotics					
ETX2514 plus sulbactam	✓	✓	✓	-	-
WCK 4234 plus meropenem (WCK-5999)	✓	-	-	-	-
LN-1-255 plus meropenem-imipenem	✓	-	-	-	-
VNRX-5113 (partner β-lactam unspecified)	✓	✓	-	-	-
WCK 5153 plus sulbactam	✓	-	-	-	-
Zidebactam plus cefepime	✓	✓	-	-	-
New β-lactam antibiotics					
AIC-499 (partner β-lactam inhibitor unspecified)	✓	✓	-	-	-
FSI-1671 plus sulbactam	✓		-	-	-
Polymyxin B-derived molecules					
SPR741	✓	✓	-	-	-
FADDI-287	✓	-	-	-	-
Aminoglycosides					
Apramycin	✓	-	-	-	-
Other drug candidates					
LpxC inhibitors	✓	-	-	-	-
RX-P873	✓	-	-	-	-
Other therapeutic options					
Bacteriophage therapy	✓	✓	✓	✓	-
Monoclonal antibodies					
C8	✓	-	-	-	-
AR-401	✓	-	-	-	-

[a]-, terminated and under review.

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Journal of Antimicrobial Chemotherapy

Pharmacodynamics of fosfomycin against ESBL- and/or carbapenemase-producing Enterobacteriaceae

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Background: The increase in antibiotic resistance in Gram-negative bacteria and the limited therapeutic options due to the shortage of new antibiotics have increased the interest of the 'old' antibiotic fosfomycin in the treatment of infections. However, there are contradictory reports on the pharmacodynamics of and emergence of resistance to fosfomycin.

Methods: Time–kill assays were performed with 11 ESBL-positive and 3 ESBL-negative strains, exposing the bacteria to 2-fold static concentrations from 0.125× to 32× MIC. The sigmoid maximum effect (E_{max}) model was fitted to the time–kill curve data. Amplification of resistance over time was evaluated under various conditions of selective pressure by plating on 16× MIC plates.

Results: Fosfomycin was bactericidal for all strains within 8 h. Using the E_{max} model, no significant differences between strains were observed for the pharmacodynamic parameters. However, the large variation in Hill slope factors for *Escherichia coli* of 0.87 up to 4.02 indicates that the killing behaviour appears to be more time dependent for some strains but concentration dependent for others. In the fosfomycin-exposed cultures under low and high selective pressure ($\geq$2× MIC) the median resistance proportions between the resistant and total population increased from $\leq 2\times10^{-6}$ ($T = 0$ h) to 0.652–0.899 ($T = 24$ h). Resistance appeared stable after repeated subculturing.

Conclusions: Killing behaviour of fosfomycin does not only differ between species but also within species and may have an impact on the design of optimal dosing regimens. Although fosfomycin was bactericidal against all strains (re)growth of resistant subpopulations occurred relatively fast. This may limit the use of fosfomycin as a single drug therapy.

Bakterisidal fakat dirençli subpopülasyonların tekrar üremesi hızlı oluyor. Bu durum monoterapiyi kısıtlayabilir.

Fosfomisin - Kombinasyon

- KPC(+) Kp için imipenem, meropenem, doripenem, kolistin, netilmisin veya tigesiklin kombinasyonu %30-74 sinerjik
- MDR *P. aeruginosa* için sinerji %13-73
- *A. baumannii* için aminoglikozid, sulbaktam veya kolistin ile sinerji
- Kombinasyonlarda antagonizma yok
- Fosfomisine direnç gelişimini önlüyor

Reffert JL et al. Pharmacother 2014

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Short Communication

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

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ABSTRACT

The increasing prevalence of KPC-producing *Klebsiella pneumoniae* (KPC-Kp) strains poses a serious threat to patients. Therapeutic options are limited to colistin, fosfomycin, tigecycline and selected aminoglycosides. Although the combination of fosfomycin with other antimicrobials is recommended, data regarding possible synergistic activity in vitro and in vivo appear inconsistent. Here we report that five drug combinations (fosfomycin combined with imipenem, ertapenem, tigecycline, colistin or amikacin) had a significant additive effect against 136 KPC-Kp strains in an in vitro chequerboard assay. In addition, time–kill assays revealed that fosfomycin enhanced the bactericidal activity of the five other antimicrobial agents. Moreover, owing to its persistent bactericidal effect, the combination of fosfomycin plus amikacin is an effective therapeutic candidate for infections by KPC-producing organisms.

Fosfomisin + Amikasin en etkili kombinasyon

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Journal of Antimicrobial Chemotherapy

Pharmacodynamics of colistin and fosfomycin: a 'treasure trove' combination combats KPC-producing *Klebsiella pneumoniae*

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Objectives: KPC-producing *Klebsiella pneumoniae* are an emerging public health problem around the globe. We defined the combinatorial pharmacodynamics and ability to suppress resistance of two 'old' antibiotics, fosfomycin and colistin, in time–kill experiments and hollow-fibre infection models (HFIM).

Methods: Two KPC-2-producing *K. pneumoniae* isolates were used: one susceptible to both colistin and fosfomycin (KPC 9A: $MIC_{colistin}$ 0.25 mg/L and $MIC_{fosfomycin} \leq 8$ mg/L) and the other resistant to colistin and susceptible to fosfomycin (KPC 5A: $MIC_{colistin}$ 64 mg/L and $MIC_{fosfomycin}$ 32 mg/L). Time–kill experiments assessed an array of colistin and fosfomycin concentrations against both isolates. Colistin and fosfomycin pharmacokinetics from critically ill patients were simulated in the HFIM to define the pharmacodynamic activity of humanized regimens over 5 days against KPC 9A.

Results: In time–kill experiments, synergy was demonstrated for all colistin/fosfomycin combinations containing >8 mg/L fosfomycin against the double-susceptible KPC strain, 9A. Synergy versus KPC strain 5A was only achieved at the highest concentrations of colistin (4 mg/L) and fosfomycin (512 mg/L) at 48 h. In the HFIM, colistin or fosfomycin monotherapies resulted in rapid proliferation of resistant subpopulations; KPC 9A regrew by 24 h. In contrast to the monotherapies, the colistin/fosfomycin combination resulted in a rapid 6.15 $\log_{10}$ cfu/mL reduction of KPC 9A by 6 h and complete suppression of resistant subpopulations until 120 h.

Conclusions: Colistin and fosfomycin may represent an important treatment option for KPC-producing *K. pneumoniae* otherwise resistant to traditional antibiotics.

Kolistin + Fosfomisin Sinerjik

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In vitro activity of fosfomycin in combination with imipenem, meropenem, colistin and tigecycline against OXA 48–positive *Klebsiella pneumoniae* strains☆,☆☆

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ABSTRACT

Carbapenem resistance due to OXA-48 enzymes in *Klebsiella pneumoniae* is increasing particularly in the Middle Eastern and European regions. Treatment options are limited. The aim of this study was to evaluate the in vitro synergistic activity of fosfomycin in combination with imipenem, meropenem, colistin and tigecycline against OXA-48 producing *K. pneumoniae* strains.

Twelve carbapenem-resistant OXA-48 producing *K. pneumoniae* isolates were enrolled in this study. Synergistic activity of fosfomycin combined with imipenem, meropenem, colistin, and tigecycline was assessed by chequerboard method.

The combination of fosfomycin was synergistic with imipenem, meropenem and tigecycline with the ratios of 42%, 33%, and 33%, respectively. Whilst the combination of fosfomycin with colistin was fully antagonistic against all of the strains, there was no statistically significant difference between the in vitro synergistic activities of fosfomycin in combination with imipenem, meropenem and tigecycline combinations ($P > 0.05$). Fosfomycin in combination with other agents can be preferred against multidrug resistant *K. pneumoniae* strains.

Kolistin + Fosfomisin antagonistik

Sunday AAR-611

In vitro synergistic activity of fosfomycin in combination with meropenem and amikacin against OXA and/or NDM-producing *K.pneumoniae* strains

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Introduction: Carbapenem resistance is a significant problem for treatment of many MDR pathogens and fosfomycin (FOS) may be a good alternative agent for combination therapies against these pathogens including Carbapenem resistance *K.pneumoniae* (CRKp). We evaluated in vitro synergistic activity of FOS in combination with meropenem (MRP) and amikacin (AMK) against CRKp blood isolates producing OXA and/or NDM.

Methods: All of the strains were resistant to MRP, 7 of which were also resistant to AMK and 7 were resistant to all. Synergy was observed in 15 (88%) isolates with MRP/FOS. Six out of 7 triple resistant strains showed synergy to MRP/FOS.

Results: All of the strains were resistant to MRP, 7 of which were also resistant to AMK and 7 were resistant to all. Synergy was observed in 15 (88%) isolates with MRP/FOS. Six out of 7 triple resistant strains showed synergy to MRP/FOS.

Conclusions: MRP/FOS combination demonstrated synergistic activity against CRKp bloodstream infections even when all strains were resistant to MRP.

Introduction

Carbapenem resistance in *Enterobacteriaceae* (especially *K.pneumoniae*) has increased globally in the last decade. OXA-48, which was the predominant carbapenemase in Turkey for years is still common, whereas NDM-1 is rapidly increasing. Carbapenem resistance *K.pneumoniae* (CRKp) strains have multiple drug resistances and limited treatment choices. Fosfomycin (FOS) may be a good alternative agent for combination therapies as it is effective against many MDR pathogens including CRKp. Most of the in-vitro synergy studies were done using KPC producing isolates, studies with other carbapenemases are limited.

The aim of this study is to evaluate the in vitro synergistic activity of FOS in combination with meropenem (MRP) and amikacin (AMK) against CRKp blood isolates producing OXA and/or NDM.

Methods

Seventeen CRKp blood isolates with different resistance patterns were included in the study (5 OXA-48 like, 7 OXA-48+NDM, 5 NDM). The minimum inhibitory concentrations (MIC) of MRP and AMK were determined by broth microdilution while agar dilution method was used for FOS. The results were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST). The checkerboard method and time-kill assay were used to assess the interactions of combinations. Agar dilution was performed in checkerboard assessment of in vitro synergistic activity of FOS in combination with MRP and AMK. The fractional inhibitory concentration index (FICI) was interpreted as follows: synergy, ≤0.5; indifference, >0.5 but ≤ 4; antagonism > 4. Three strains which have different carbapenemases were selected to undergo time-kill assays with MRP/FOS combination. Samples were taken at 0, 4, 8, 24h. Synergy was defined as ≥2 $\log_{10}$ decrease in CFU/mL between the combination and its most active constituent.

Results

All of the strains wer. e resistant to MRP, 7 of which were also resistant to AMK and 7 were resistant to all. Synergy was observed in 15 (88%) isolates with MRP/FOS. Six out of 7 triple resistant strains showed synergy to MRP/FOS. No antagonism was observed with any combinations. The time-kill assay demonstrated that MRP/FOS combination exhibited synergistic activity at 24 hours for all three strains. Table 1 shows MIC values of isolates, synergistic effect of combinations and time-kill assay results.

Table 1. Checkerboard results obtained with fosfomycin in combination with meropenem and amikacin against 17 CRKp blood isolates

	Carbapenemase	MIC values (µg/mL)			FOS/MRP		FOS/AMK		Time-kill results
		FOS	MRP	AMK	Activity	FICI	Activity	FICI	$\log_{10}$ reduction in CFU/Ml at 24h
1	OXA-48	>256	16	16	I	0,51	I	1,24	
2	OXA-48+NDM	16	128	2560	S	**0,36**	S	**0,05**	
3	NDM	16	64	>5120	S	**0,20**	Indeterminacy[a]		
4	OXA-48	16	16	64	I	0,81	I	0,86	
5	NDM	64	64	4096	S	**0,39**	I	0,75	>4
6	NDM	8	64	>5120	S	**0,35**	Indeterminacy[a]		
7	NDM	256	256	2560	S	**0,48**	I	0,75	
8	OXA-48+NDM	64	256	2560	S	**0,44**	I	0,80	
9	OXA-48	32	64	512	S	**0,26**	S	**0,29**	>4
10	OXA-48+NDM	64	64	4608	S	**0,33**	I	0,77	
11	OXA-48	16	32	256	S	**0,07**	S	**0,15**	
12	OXA-48	32	16	8	S	**0,29**	I	1,80	
13	OXA-48+NDM	256	512	>5120	S	**0,42**	Indeterminacy[a]		
14	NDM	32	64	4608	S	**0,12**	S	**0,24**	
15	OXA-48+NDM	64	64	2560	S	**0,18**	S	**0,38**	>4
16	OXA-48	16	16	2	S	**0,23**	I	1,35	
17	OXA-48	32	16	4	S	**0,32**	I	1,70	

[a] Three results were not interpretable due to off-scale MICs and labeled indeterminate in FOS/AMK combination S; Synergy (FICI ≤0.5), I; Indifference (FICI >0.5 but ≤4), A; Antagonism (FICI >4), Indeterminacy; FICI not interpretable

Conclusions

MRP/FOS combination demonstrated synergistic activity against CRKp bloodstream infections even when all strains were resistant to MRP, which is promising given limited available treatment options especially against OXA-48 and NDM, the two common species in Turkey.

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Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

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ABSTRACT

Fosfomycin is active in vitro against extensively drug-resistant (XDR) and pandrug-resistant (PDR) *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* carbapenemase-producing strains; however, the in vivo effectiveness against such pathogens is almost unknown. A multicentre, observational, prospective case-series study was performed in 11 ICUs. All consecutive fosfomycin-treated patients suffering from XDR or PDR fosfomycin-susceptible, microbiologically documented infections were recorded. Clinical and microbiological outcomes were assessed. A safety analysis was performed. In total, 68 patients received fosfomycin during the study period, 48 of whom were considered suitable for effectiveness analysis based on predefined criteria. Bacteraemia and ventilator-associated pneumonia were the main infections. Carbapenemase-producing *K. pneumoniae* and *P. aeruginosa* were isolated in 41 and 17 cases, respectively. All isolates exhibited an XDR or PDR profile, being fosfomycin-susceptible by definition. Fosfomycin was administered intravenously at a median dose of 24 g/day for a median of 14 days, mainly in combination with colistin or tigecycline. Clinical outcome at Day 14 was successful in 54.2% of patients, whilst failure, indeterminate outcome and superinfection were documented in 33.3%, 6.3% and 6.3%, respectively. All-cause mortality at Day 28 was 37.5%. Bacterial eradication was observed in 56.3% of cases. Fosfomycin resistance developed in three cases. The main adverse event was reversible hypokalaemia. In conclusion, fosfomycin could have a place in the armamentarium against XDR and PDR Gram-negative infections in the critically ill. Resistance development during therapy, which has been a matter of concern in previous studies, did not occur frequently. The necessity of combination with other antibiotics requires further investigation.

- Prospektif olgu serisi, ÇM, YBÜ
- 48 hasta
- %65.2 ağır sepsis veya septik şok
- Enfeksiyonların dağılımı

Primer bakteriyemi	18(%37.5)
KİKDE	7(%14.6)
VİP	14(%29.2)
İAİ	7(%14.6)

- %60.4 monomikrobiyal
- 41 hastada KPC-2 Kp(23 monomikrobiyal, 18 polimikrobiyal)
- Kp: XDR 26/41, PDR 15/41
- Pa: VİM-2, 16/17 XDR

- Tüm izolatlar fosfomisin duyarlı(E-test, MİK ≤ 64 mg/L)
- 32 hastada fosfomisin + kolistin
- 19 hastada fosfomisin + tigesiklin
- 15 hastada fosfomisin +gentamisin
- 12 hastada fosfomisin + meropenem
- 4 hastada fosfomisin + Pip/Tazo

- Fosfomisin 18 hastada tek antibiyotikle kombine
- Ortanca doz 24 g/gün
- RRT'de ortanca doz 16 g/gün
- Ortanca tedavi süresi 14 gün

- 28. gün mortalitesi 18(%37.5)
- 3 hastada direnç gelişmiş

Table 4

Patient outcomes in the effectiveness population ($n = 48$).[a]

Infection	Clinical outcome at Day 14				Microbiological outcome at Day 14			All-cause mortality	
	Successful	Failure	Superinfection	Indeterminate	Eradication	Persistence	Indeterminate	Day 14	Day 28
Primary bacteraemia ($n = 18$)	11 (61.1)	6 (33.3)	0	1 (5.6)	13 (72.2)	4 (22.2)	1 (5.6)	4 (22.2)	7 (38.9)
CR-BSI ($n = 7$)	1 (14.3)	3 (42.9)	2 (28.6)	1 (14.3)	3 (42.9)	1 (14.3)	3 (42.9)	4 (57.1)	4 (57.1)
VAP ($n = 12$)	8 (66.7)	3 (25.0)	1 (8.3)	0	5 (41.7)	4 (33.3)	3 (25.0)	2 (16.7)	4 (33.3)
VAP + IAI ($n = 1$)	1 (100)	0	0	0	1 (100)	0	0	0	0
VAP + pleural empyema ($n = 1$)	1 (100)	0	0	0	0	1 (100)	0	0	0
UTI ($n = 1$)	1 (100)	0	0	0	0	0	1 (100)	0	0
IAI ($n = 6$)	3 (50.0)	2 (33.3)	0	1 (16.7)	3 (50.0)	3 (50.0)	0	1 (16.7)	3 (50.0)
Lung abscess ($n = 1$)	0	1 (100)	0	0	1 (100)	0	0	0	0
Meningitis ($n = 1$)	0	1 (100)	0	0	1 (100)	0	0	0	0
Total ($n = 48$)	26 (54.2)	16 (33.3)	3 (6.3)	3 (6.3)	27 (56.3)	13 (27.1)	8 (16.7)	11 (22.9)	18 (37.5)

CR-BSI, catheter-related bloodstream infection; VAP, ventilator-associated pneumonia; IAI, intra-abdominal infection; UIT, urinary tract infection.

[a] Data are no. (%) of patients.

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Journal of Hospital Infection

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

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

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G

S U M M A R Y

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.

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

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

The most common primary diagnosis in the study patients was cardiovascular disease, followed by solid organ and haematological malignancies (Table II). On univariate analysis, numerous factors were found to be associated with fatality (Table II). On multi-variate analysis, age >70 years, central-catheter-related infections, ventilator-associated pneumonia, APACHE II score, MIC of carbapenems and MIC of colistin were included as the independent variables. The MICs of 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 the only factors that were significantly associated with fatality. The logistic regression model predicted fatality with sensitivity of 74% (area under receiver operating characteristic curve was 74%).

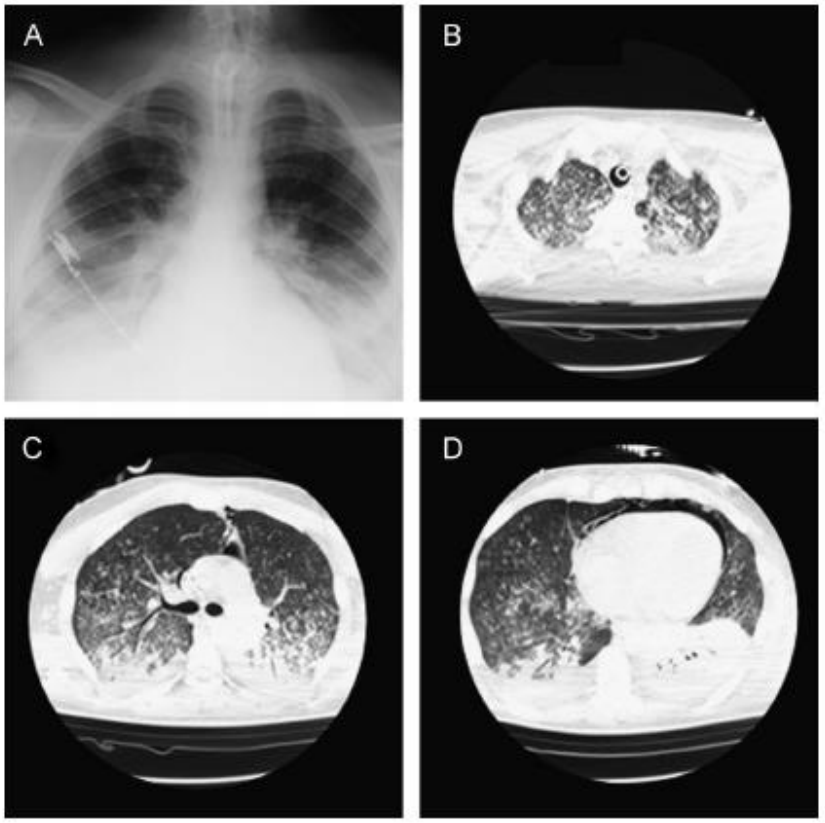
Kolistin Dirençli Kp - VİP

Table 2 – Antibiotic susceptibility test on bronchoalveolar lavage positive for KPC-Kp.

Antibiotic[a]	Vitek-2® (MIC μg/ml)	E-test (MIC μg/ml)
Amikacin	>16	32
Colistin	>16	4
Cotrimoxazole	–	>32
Fosfomycin	–	16
Gentamicin	4	2
Imipenem	>16	16
Meropenem	>16	8
Tigegycline	2	2

KPC-Kp, *Klebsiella pneumoniae* producing KPC-type carbapenemase; MIC, minimum inhibitory concentration.

[a] Susceptibility was determined in accordance to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.



Kolistin Dirençli Kp - VİP

- Tigesiklin 2x100 mg
  + Fosfomisin 3x3 g
  + Kolistin 2x4.5 MIU
- 9 günlük tedavi ile iyileşme

Viaggi B et al. Respir Invest 2015

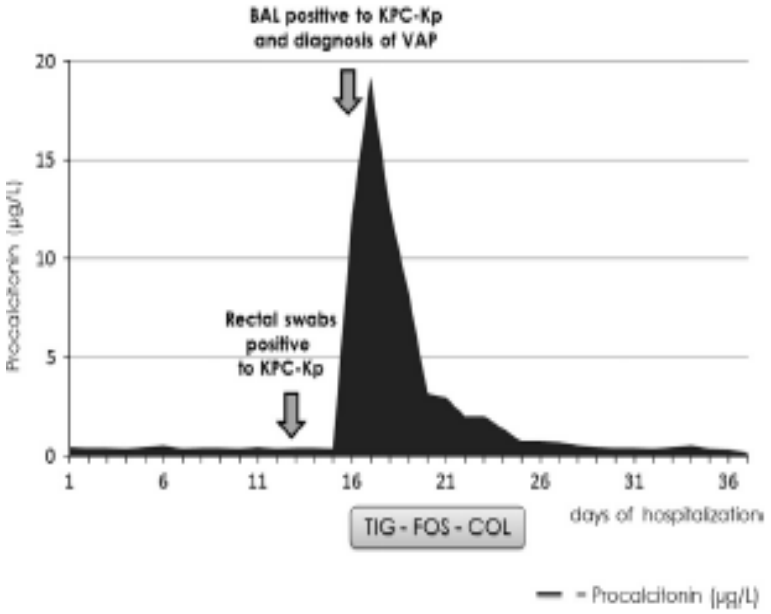


Fig. 2 – Time-course of serum procalcitonin concentration and antibiotic administrations in the intensive care unit. COL: colistin, FOS: fosfomycin, TIG: tigecycline, BAL: bronchoalveolar lavage, KPC-Kp: *Klebsiella pneumoniae* producing KPC-type carbapenemase.

Kolistin-R ve Karbapenem-R Kp

- Kolistin + Tigesiklin sinerjik

  Betts Jwet al. Antimicrob Agents Chemother 2014

- Kolistin + Ertapenem + Meropenem hızlı bakterisidal etki

  Oliva A et al. Int J Infect Dis 2015
  Oliva A et al. J Infect 2016

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Synergistic Activity of Colistin-Containing Combinations against Colistin-Resistant *Enterobacteriaceae*

Thea Brennan-Krohn,[a,b,d] Alejandro Pironti,[c] James E. Kirby[a,d]

TABLE 2 Rates of synergy by drug using checkerboard array

Drug tested in combination with colistin	% synergy[a] (95% confidence interval) for: All strains	Strains excluding species intrinsically resistant to colistin
Linezolid	95.0 (73.1–99.7)	100 (78.1–100.0)
Rifampin	94.7 (71.9–99.7)	100 (77.1–100.0)
Azithromycin	90.0 (66.9–98.2)	100 (78.1–100.0)
Fusidic acid	90.0 (66.9–98.2)	94.4 (70.6–99.7)
Minocycline	85.0 (61.1–96.0)	88.9 (63.9–98.1)
Clindamycin	80.0 (55.7–93.4)	88.9 (63.9–98.1)
Erythromycin	80.0 (55.7–93.4)	88.9 (63.9–98.1)
Chloramphenicol	75.0 (50.6–90.4)	77.8 (51.9–92.6)
Levofloxacin	70.0 (36.4–80.0)	66.7 (41.2–85.6)
Doxycycline	60.0 (36.4–80.0)	66.7 (41.2–85.6)
Ceftazidime-avibactam	41.2 (19.4–66.5)	46.7 (22.3–72.6)
Tigecycline	25.0 (9.6–49.4)	27.8 (10.7–53.6)
Vancomycin	25.0 (9.6–49.4)	27.8 (10.7–53.6)
Tetracycline	20.0 (6.6–44.3)	22.2 (7.4–48.1)
Meropenem	15.0 (4.0–38.9)	11.1 (1.9–36.1)
Amikacin	15.0 (4.0–38.9)	16.7 (4.4–42.3)
Trimethoprim-sulfamethoxazole	15.0 (4.0–38.9)	11.1 (1.9–36.1)
Apramycin	10.0 (1.8–33.1)	11.1 (1.9–36.1)
Daptomycin	0.0 (0–22.9)	0.0 (0.0–25.3)

[a]Synergy percentages represent the results of testing of 20 isolates for each combination, except rifampin (results of testing of 19 isolates were used because 1 trial had skipped wells), daptomycin (results for testing of 17 isolates were used because 1 trial had skipped wells and 2 trials had colistin MICs >±1 2-fold dilution from the modal MIC), and ceftazidime-avibactam (results for 17 isolates were used because 3 trials had colistin MICs >±1 2-fold dilution from the modal MIC).

Mortality Associated with Bacteremia Due to Colistin-Resistant *Klebsiella pneumoniae* with High-Level Meropenem Resistance: Importance of Combination Therapy without Colistin and Carbapenems

Isabel Machuca,[a] Belén Gutiérrez-Gutiérrez,[b] Irene Gracia-Ahufinger,[c] Francisco Rivera Espinar,[d] Ángela Cano,[a] Julia Guzmán-Puche,[c] Elena Pérez-Nadales,[a] Clara Natera,[a] Marina Rodríguez,[d] Rafael León,[d] Juan J. Castón,[a] Fernando Rodríguez-López,[c] Jesús Rodríguez-Baño,[b] Julián Torre-Cisneros[a]

August 2017 Volume 61 Issue 8 e00406-17 Antimicrobial Agents and Chemotherapy

ABSTRACT Combination therapy including colistin and a carbapenem has been found to be associated with lower mortality in the treatment of bloodstream infections (BSI) due to KPC-producing *Klebsiella pneumoniae* when the isolates show a meropenem or imipenem MIC of <16 mg/liter. However, the optimal treatment of BSI caused by colistin- and high-level carbapenem-resistant KPC-producing *K. pneumoniae* is unknown. A prospective cohort study including episodes of bacteremia caused by colistin-resistant and high-level meropenem-resistant (MIC ≥ 64 mg/liter) KPC-producing *K. pneumoniae* diagnosed from July 2012 to February 2016 was performed. The impact of combination therapy on crude 30-day mortality was analyzed by Cox regression using a propensity score as a covariate to control for indication bias and in an inverse probability of treatment weighting (IPTW) cohort. The study sample comprised 104 patients, of which 32 (30.8%) received targeted monotherapy and 72 (69.2%) received targeted combination therapy; none of them received either colistin or a carbapenem. The 30-day crude mortality rate was 30.8% (43.8% in patients treated with monotherapy and 25% in patients receiving combination therapy). In the Cox regression analysis, 30-day mortality was independently associated with septic shock at BSI onset (hazard ratio [HR], 6.03; 95% confidence interval [CI], 1.65 to 21.9; $P = 0.006$) and admission to the critical care unit (HR, 2.87; 95% CI, 0.99 to 8.27; $P = 0.05$). Targeted combination therapy was associated with lower mortality only in patients with septic shock (HR, 0.14; 95% CI, 0.03 to 0.67; $P = 0.01$). These results were confirmed in the Cox regression analysis of the IPTW cohort. Combination therapy is associated with reduced mortality in patients with bacteremia due to colistin-resistant KPC-producing *K. pneumoniae* with high-level carbapenem resistance in patients with septic shock.

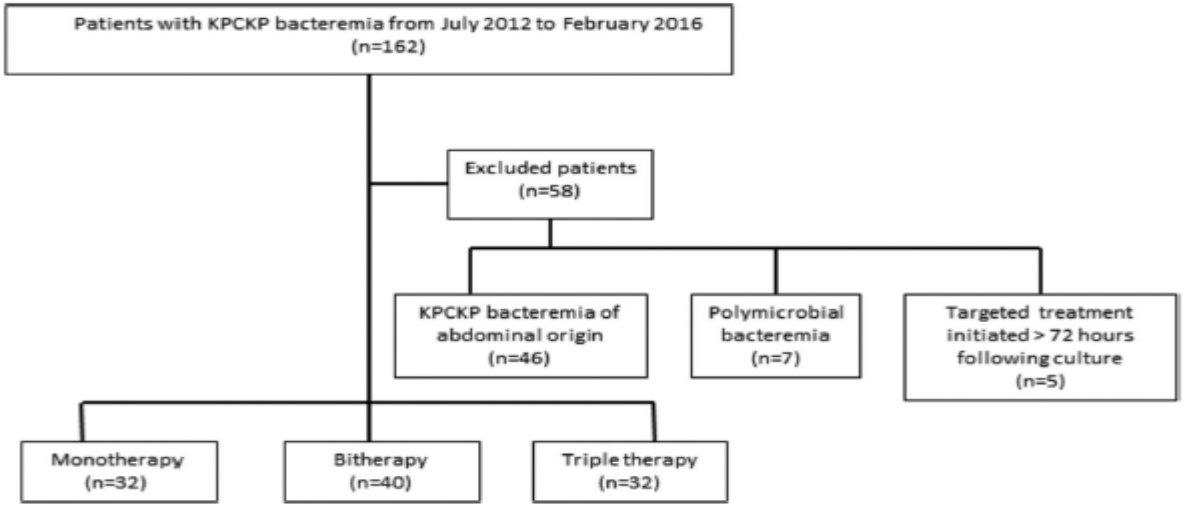


FIG 1 Study flow diagram.

TABLE 3 Outcome of patients with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance according to treatment regimen

Treatment regimen	No. dead/treated	Mortality (%)
Monotherapy		
Tigecycline	8/15	53.3
Gentamicin	4/9	44.4
Fosfomycin	2/8	25
Total for monotherapy	14/32	43.8
Combination therapy		
Tigecycline + gentamicin	3/13	23.1
Tigecycline + fosfomycin	6/16	37.5
Gentamicin + fosfomycin	3/11	27.3
Tigecycline + fosfomycin + gentamicin	6/32	18.8
Total for combination therapy	18/72	25

Kolistin-R ve Yüksek Düzeyde Meropenem Dirençli Kp Bakteriyemisi

- Kolistin ve karbapenem içermeyen kombinasyonlar
- Monoterapi 14/32(%43.8 mortalite)
  - -Tigesiklin
  - -Gentamisin
  - -Fosfomisin
- Kombinasyon 18/72(%25 mortalite)
  - -Tigesiklin + Gentamisin
  - -Tigesiklin + Fosfomisin
  - -Gentamisin + Fosfomisin
  - -Tigesiklin + Fosfomisin + Gentamisin
- Septik şoklu hastalarda kombinasyon yararlı($p<0.001$)

Machura I et al. Antimicrob Agents Chemother 2017

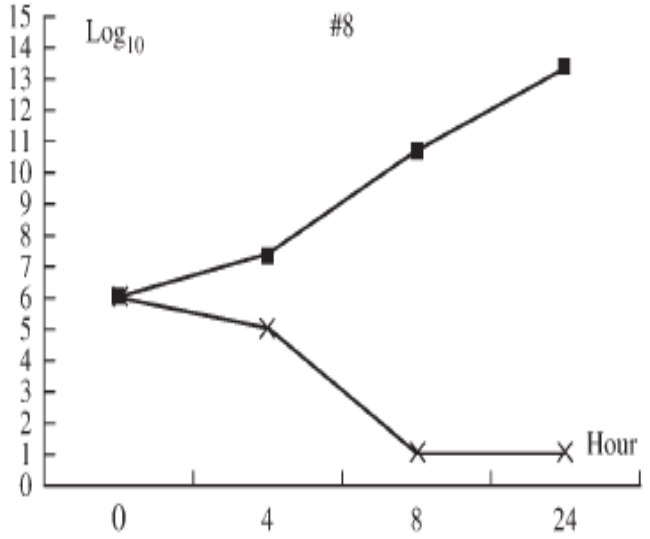
A.baumannii - Heterodirenç

- Hacettepe Üniv. Tıp Fakültesi
- 200 *A.baumannii*
- Kolistin direnci %29
- Heterodirenç saptanmamış

Çağlan E ve ark. Yüksek Lisans Tezi, 2017

Karbapenem R - *A. baumannii*

Antibiotics	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Imipenem[a]	32	32
Colistin[b]	1	1
Tigecycline[c]	2	4
Sulbactam[d]	16	32
Rifampicin[e]	4	4



- IMP + Sulbaktam

  7/8 sinerji

Song JY et al. J Antimicrob Chemother 2007

Sulbaktam - Tedavi

- İmipenem dirençli *A.baumannii* enfeksiyonu
  -Ampisilin/Sulbaktam %67.5 klinik yanıt

Levin AS et al. Int J Antimicrob Agents 2003

- Yüksek doz Ampisilin/Sulbaktam, Kolistin kadar etkili

Betrosian AP et al. J Infection 2008

Sulbaktam + Kolistin

- Meropenem ve sulbaktam dirençli *A. baumannii* menenjitinde tedaviye kolistin eklenmesi serum ve BOS bakterisidal aktivitesini artırmış

- *A. baumannii* : Sulbaktam ve Meropenem dirençli
- Kolistin + Sulbaktam, tek başına kolistine ve diğer kombinasyonlara göre daha etkili

Lee CH et al. Microb Drug Resist 2008

Sulbaktam - *A.baumannii*

- Sulbaktam MİK'leri(direnci) giderek artıyor

  Dağı HT ve ark. Mikrobiyoloji Bul 2014
  Dafopoulou K et al. J Med Microbiol 2018
  Betrosian AP et al. J Infection 2008

- Sulbaktamın etkisi MİK'ten(dirençten) bağımsız

  Oliveira MS et al. Clinics 2013

- Çalışmalarda Sulbaktam dozu: 4-12 g/gün

  Jimenez-Mejias ME et al. Clin Infect Dis 1997
  Levin AS et al. Int J Antimicrob Agents 2003
  Betrosian AP et al. J Infection 2008
  Betrosian AP et al. Scand J Infect Dis 2007

Sulbaktam - *A.baumannii*

- Kritik hastalarda ve dirençli *A.baumannii* infeksiyonlarında 2-4 g/gün ile klinik başarı düşük
- Yüksek dozlarda kolistin ile aynı düzeyde
- Kritik hastalarda ve MDR: 6 g/gün veya daha yüksek olmalı
- Sulbaktam/Ampisilin ile imipenem, meropenem, fosfomisin, rifampisin ve kolistin kombinasyonu sinerjik
- Meropenem + Sulbaktam + Kolistin: Çok yüksek düzeyde sinerji

Adnan S et al. Int J Antimicrob Agents 2013

Sulbaktam - *A.baumannii*

- Ventilatörle ilişkili pnömonide ampisilin/sulbaktam = kolistin

  Zalts R et al. Am J Ther 2016

- Ventilatörle ilişkili pnömonide meropenem + kolistin = meropenem + ampisilin/sulbaktam

  Khalili H et al. J Comp Eff Res 2018

- Ventilatörle ilişkili pnömonide, sulbaktam MİK'leri yüksek olsa bile kolistin + karbapenem = kolistin + sulbaktam(6 g/gün)

  Ungthammakhun C et al. Infect Drug Resist 2019

Karbapenem Dirençli *Acinetobacter baumannii*

- Kolistin: Kombinasyon? Monoterapi?

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

Acinetobacter baumannii - Kolistin

- KDE: Kombinasyon ile monoterapi arasında fark yok

Lopez-Cortes LE et al. J Antimicrob Chemother 2014

- KDE ve VİP: Kombinasyon ile monoterapi arasında fark yok

Şimşek F et al. Indian J Med Microbiol 2012

- VİP: Kolistin ile kolistin + sulbaktam arasında fark yok

Kalın G et al. Infection 2014

Acinetobacter baumannii - Kolistin

- Ciddi enfeksiyonlar: Kolistin ile kolistin + rifampisin kombinasyonu arasında fark yok

Durante-Mangoni E, et al. Clin Infect Dis 2013

- VİP: Kolistin ile kolistin + rifampisin kombinasyonu arasında fark yok

Aydemir H et al. Epidemiol Infect 2013

Meta-Analiz Sonuçları

- Kombinasyonun üstün olduğunu destekleyen kuvvetli kanıt yok

  Liu Q et al. PLOS ONE 2014

- Ağır enfeksiyonlarda kombinasyon tercih edilebilir

  Poulikakos P et al. Eur J Clin Microbiol Infect Dis 2014

- VİP:Kombinasyon monoterapiden üstün değil

  Gu W-J et al. Int J Antimicrob Agents 2014

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

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

Summary

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

Lancet Infect Dis 2018

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

Kolistin
Monoterapi - Kombinasyon

- Açık etiketli, randomize, kontrollü
- Karbapenem dirençli GNB
- Erişkin hastalar
- Bakteriyemi, VİP, HGP, Ürosepsis
- 406 hasta
- %87(355/406) pnömoni veya bakteriyemi
- %77(312/406) *A baumannii*

Paul M et al. Lancet Infect Dis 2018

Kolistin
Monoterapi - Kombinasyon

- Tedavi başarısı
  -Yaşamda kalma
  -Hemodinamik stabilite
  -SOFA skorunun stabil kalması ya da iyileşmesi
  -PaO2/FiO2 oranının stabil kalması ya da iyileşmesi(pnömonide)
  -Mikrobiyolojik kür(bakteriyemide)
- Klinik başarısızlık: Tüm başarı kriterlerinde buluşulamaması(14. günde)

	Colistin (n=198)	Colistin and meropenem (n=208)
(Continued from previous page)		
Appropriate empirical antibiotic treatment within 2 days*	106 (54%)	103 (50%)
48-h mortality	12 (6%)	15 (7%)
Modification of assigned regimen in first 5 days	17 (9%)	8 (4%)
Receipt of additional antimicrobials permitted by protocol		
Glycopeptide or daptomycin	29 (15%)	22 (11%)
Other antibacterial†	14 (7%)	11 (5%)
Antifungal	4 (2%)	5 (2%)
Total cumulative colistin for patients alive on day 14 (million units)	99·0 (72·0–135·0), n=134	106·5 (72·5–153·0), n=138
Receipt of nephrotoxic medications during treatment‡	87 (44%)	94 (45%)

Data are mean (SD), n (%), or median (IQR). n values indicated for outcomes assessed only for survivors, or if patient data are missing. BMI=body-mass index. SOFA=Sequential Organ Failure Assessment. *Covering treatment given in the first 48 h of infection, before reporting of final culture results. †Other antibacterials include penicillins, linezolid, cefazolin, or metronidazole. ‡Including non-steroidal anti-inflammatory drugs, aciclovir, ganciclovir or foscarnet, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, ciclosporin, tacrolimus, amphotericin B, methotrexate, or cisplatin.

Table 1: **Patient and infection characteristics**

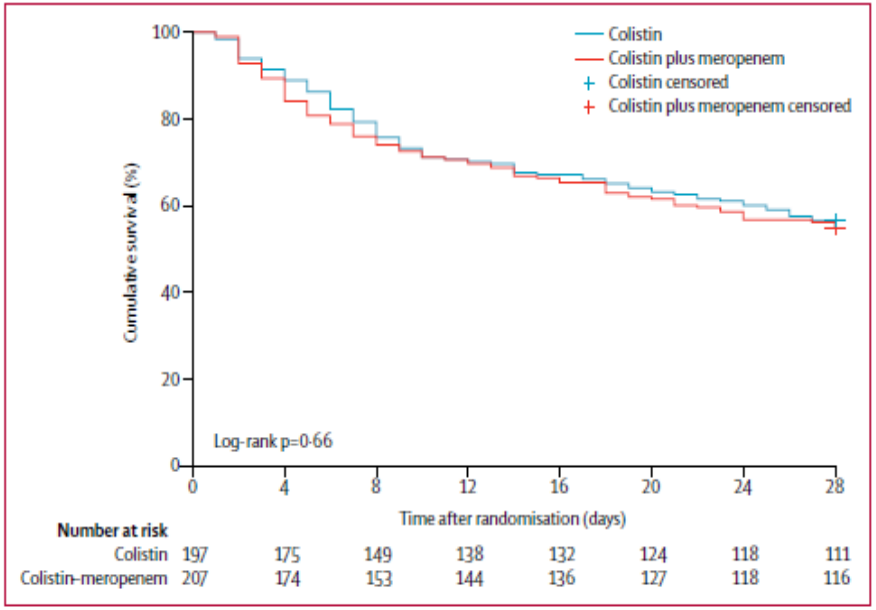


Figure 2: **Survival analysis to day 28 after randomisation**

	Colistin (n=198)	Colistin and meropenem (n=208)	p value
Adverse event requiring treatment discontinuation	3 (2%)	4 (2%)	1·0
Creatinine on day 7, mg/dL	1·30 (0·69–2·15), n=161	1·12 (0·56–2·40), n=162	0·258
RIFLE score day 14 compared with randomisation*	n=124	n=125	0·001†
None	64 (52%)	89 (71%)	..
Risk	20 (16%)	18 (14%)	..
Injury	17 (14%)	7 (6%)	..
Failure	21 (17%)	10 (8%)	..
Loss	2 (2%)	1 (1%)	..
Creatinine on day 14, mg/dL	1·49 (0·80–2·60), n=124	1·08 (0·56–1·98), n=162	0·007
RIFLE score day 28 compared with randomisation*	n=77	n=88	0·075†
None	50 (65%)	70 (80%)	..
Injury	5 (6%)	5 (6%)	..
Failure	12 (16%)	4 (4%)	..
Loss	10 (13%)	8 (9%)	..
End-stage kidney disease	0	1 (1%)	..
Creatinine on day 28, mg/dL	1·13 (0·65–1·87), n=75	1·00 (0·60–1·84), n=82	0·544
Diarrhoea	32 (16%)	56 (27%)	0·009
Clostridium difficile infection	2 (1%)	6 (3%)	0·174
Seizures	6 (3%)	5 (2%)	0·698

Data are n (%) or median (IQR). n values indicated for outcomes assessed only for survivors or in a specific patient subgroup, or if patient data are missing. *Among patients not on haemodialysis at randomisation, alive with renal function tests available. †p for trend.

Table 3: Adverse events

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

n values indicated for outcomes assessed in a specific patient subgroup. *Surviving 48 h and no modification in the first 5 days after randomisation. †No covering treatment until day 3 after culture taken. Appropriate empirical antibiotic treatment consisted of colistin in all but nine patients who received aminoglycosides (three patients), co-trimoxazole, tigecycline, ampicillin–sulbactam, minocycline, gentamicin plus chloramphenicol and gentamicin plus tigecycline (one patient each). ‡Includes polymicrobial infections in which at least one of the carbapenem-resistant Gram-negative bacteria were Enterobacteriaceae; 66 of 72 patients had *Klebsiella pneumoniae* infections. §Includes *Pseudomonas aeruginosa* and *A baumannii* polymicrobial infections; 19 of 21 patients had *P aeruginosa* infections. Unstratified analysis due to small numbers.

Table 4: **Subgroup analyses**

Kolistin
Monoterapi - Kombinasyon

- *A baumannii* için tedavi kollarında fark yok
- Kombinasyon kolunda daha fazla diyare
- Kombinasyon kolunda daha az hafif böbrek yetmezliği

Journal of Infection 79 (2019) 130–138

Contents lists available at ScienceDirect

Journal of Infection

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

Bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*: Clinical features, therapy and outcome from a multicenter study

Alessandro Russo[a], Matteo Bassetti[a], Giancarlo Ceccarelli[b], Novella Carannante[c], Angela Raffaella Losito[d], Michele Bartoletti[e], Silvia Corcione[f], Guido Granata[g], Antonella Santoro[h], Daniele Roberto Giacobbe[i,j], Maddalena Peghin[a], Antonio Vena[a], Francesco Amadori[k], Francesco Vladimiro Segala[f], Maddalena Giannella[e], Giovanni Di Caprio[c], Francesco Menichetti[k], Valerio Del Bono[l], Cristina Mussini[h], Nicola Petrosillo[g], Francesco Giuseppe De Rosa[f], Pierluigi Viale[e], Mario Tumbarello[d], Carlo Tascini[c], Claudio Viscoli[i,j], Mario Venditti[b,*], ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

Table 2
Cox regression analysis about risk factors associated with 14-day and 30-day mortality.

14-day mortality				30-day mortality			
Variables	HR	CI 95%	p	Variables	HR	CI 95%	p
Septic shock	10.79	1.12–141	0.04	Septic shock	1.54	1.04–2.27	0.03
Adequate source control of infection	0.22	0.01–0.42	0.01	Colistin-containing regimen	0.41	0.27–0.63	<0.001
Charlson comorbidity index > 3	1.44	1.04–2	0.02	Aminoglycoside-containing regimen	2.57	1.33–4.94	0.005
Combination therapy	0.36	0.01–0.89	0.03	Previous surgery (30 days)	1.63	1.16–2.29	0.005

HR: hazard ratio; CI: confidence interval.

PHARMACOTHERAPY

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Brian T. Tsuji,[1,*,‡] Jason M. Pogue,[2,‡] Alexandre P. Zavascki,[3,4] Mical Paul,[5,6] George L. Daikos,[7] Alan Forrest,[8] Daniele R. Giacobbe,[9,10] Claudio Viscoli,[9,10] Helen Giamarellou,[11] Ilias Karaiskos,[11] Donald Kaye,[12] Johan W. Mouton,[13] Vincent H. Tam,[14] Visanu Thamlikitkul,[15] Richard G. Wunderink,[16] Jian Li,[17,§] Roger L. Nation,[18,§] and Keith S. Kaye[19,*,§]

(Pharmacotherapy 2019;39(1):10–39) doi: 10.1002/phar.2209

XVII. Should Monotherapy or Combination Therapy for Polymyxin B or Colistin Be Used to Treat Patients with CRAB?

Recommendations. **R29**: We recommend that for invasive infections due to CRAB, polymyxin B or colistin should be used in combination with one or more additional agents to which the pathogen displays a susceptible MIC (*Best practice recommendation*; panel voted 10–5 in favor of combination).

R30: If a second active agent to which the infecting CRAB displays a susceptible MIC is unavailable, we recommend that polymyxin B or colistin should be used alone as monotherapy (*Weak recommendation, moderate quality evidence*; panel voted 8–7 in favor of monotherapy).

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Carbapenem-resistant *Acinetobacter baumannii*: in pursuit of an effective treatment

E.-T. Piperaki [1], L.S. Tzouvelekis [1], V. Miriagou [2], G.L. Daikos [3,*]

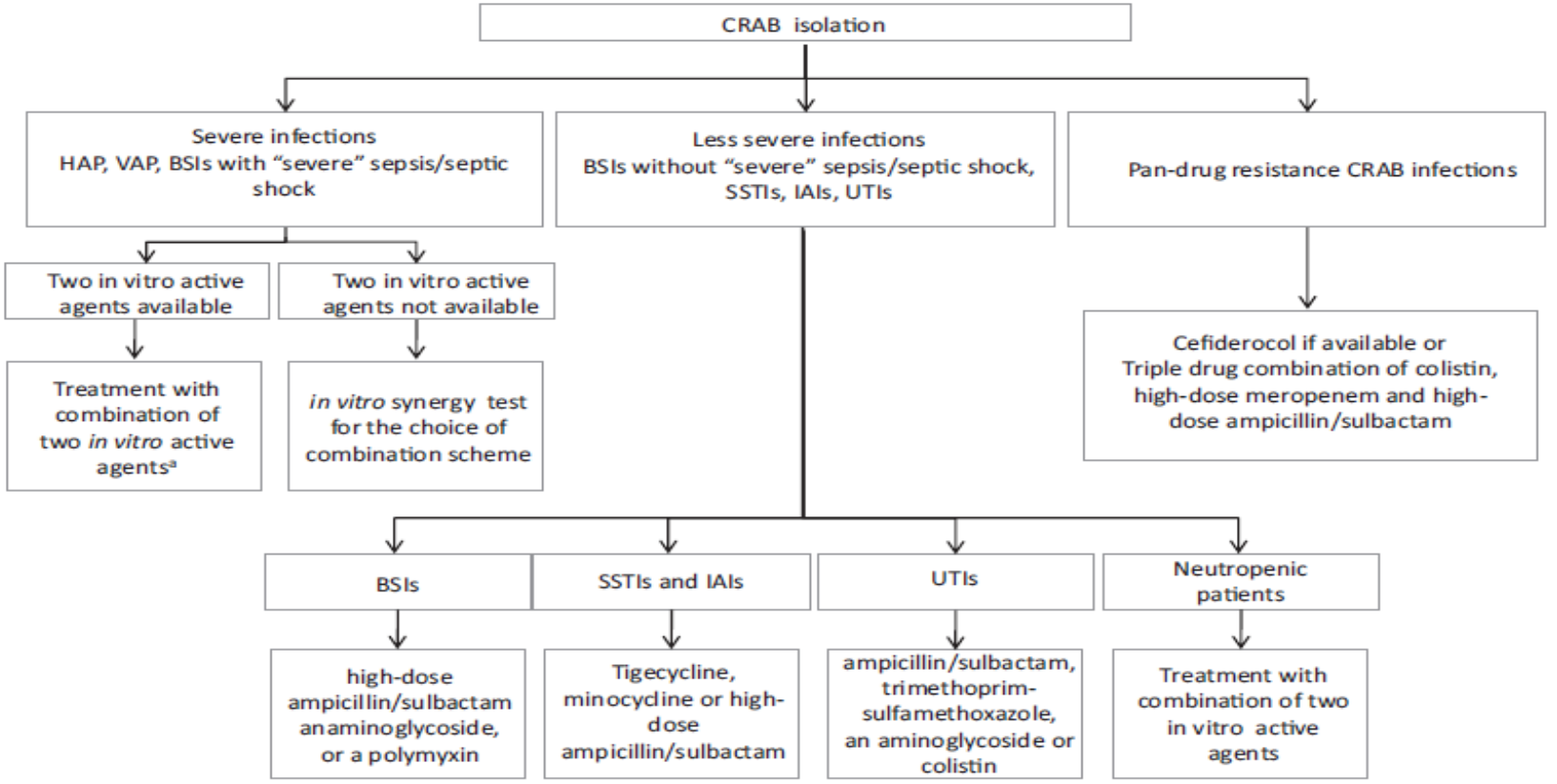


Fig. 1. Proposed therapeutic approach for carbapenem resistant *Acinetobacter baumannii* infections (CRAB).HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; BSI, bloodstream infections; SSTI, skin and soft tissue infection; IAI, intra-abdominal infection; UTI, urinary tract infection. [a] Preferable combinations: an aminoglycoside or a polymyxin with high-dose ampicillin–sulbactam or high-dose tigecycline or high-dose minocycline.

TMP/SMX - *A.baumannii*

- Eğer *A.baumannii* duyarlı ise kombinasyonun bir parçası olabilir
- Monoterapi açısından deneyim oldukça az
- Sepsis ile seyretmeyen üriner sistem infeksiyonlarında seçenek olabilir

Falagas ME et al. Int J Antimicrob Agents 2015
Raz-Pasteur A et al. J Glob Antimicrob Resist 2019

VİP: Kolistin – İnhalasyon?

Kolistin - İnhalasyon Tedavisi

- 2005-2008, ÇİD VİP tedavisi
- Retrospektif, vaka-kontrol
- Kolistin(43) ile kolistin + inhale kolistin(43) karşılaştırılması
- Sadece kolistine duyarlı *A.baumannii*, *P. aeruginosa* ve *K. pneumoniae*
- E test, ≤2 mg/L duyarlı
- Kolistin 3x3 MIU intravenöz
- Aerosol 2x1 MIU

Kofteridis DP et al. Clin Infect Dis 2010

Kolistin - İnhalasyon Tedavisi

- 66/86 *A. baumannii*
- Kolistin (IV) ortanca süresi 10(4-36) gün
- Kolistin(Aerosol + IV) ortanca süresi 13 (5-56) gün
- Bakteriyolojik eradikasyon oranları arasında fark yok
- Klinik başarı ve mortalite açısından anlamlı fark yok

Kofteridis DP et al. Clin Infect Dis 2010

Kolistin - İnhalasyon Tedavisi

- 2005-2007, Atina
- 121 VİP (92 olguda etken *A. baumannii*)
- 78 hasta(İV + inhalasyon), 18'inde etkili 3.antibiyotik
- 43 hasta sadece İV almış
- Klinik iyileşme
  - -İV + inhalasyon 62/78(%79.5)
  - -İV 26/43(%60.5),p=0.025

Korbilla IP et al. Clin Microbiol Infect 2010

Kolistin - İnhalasyon Tedavisi

- Aynı anda başka bir antibiyotik almayan grup
  - -İV + inhalasyon 46/60(%76.7)
  - -İV 22/38(%57.9),p=0.049
- Hastane içi mortalite
  - -İV + inhalasyon 31/78(%39.7)
  - -İV 19/43(%44.2),p=0.69
- Çok değişkenli analizde mortalite için risk fak.
  - -Yüksek APACHE II skoru
  - -Malignite
  - -Düşük İV kolistin/gün

Korbilla IP et al. Clin Microbiol Infect 2010

Kolistin - İnhalasyon Tedavisi

- 29 hasta IV + inhalasyon
- 16 hasta IV
- İV olarak dozlar farklı
  - -15 hasta 4x2.5 mg/kg
  - -20 hasta 2x2.5 mg/kg
  - -10 hasta düşük doz(ClCr)
- Yüksek doz ve inhalasyon yararlı bulunmamış

Kalın G et al. J Infect Chemother 2012

Kolistin - İnhalasyon Tedavisi Meta-Analiz

- 16 çalışma
- Aerosol + IV kolistin=anlamlı olarak klinik yanıt artışı sağlıyor(OR, 1.57; 95% CI, 1.14-2.15; p=0.006) fakat kanıtın kalitesi çok düşük
- Mikrobiyolojik eradikasyonda anlamlı artış sağlıyor(OR, 1.61; 95% CI, 1.11-2.35; p=0.01) fakat kanıtın kalitesi düşük

Valachis A et al. Crit Care Med 2015

International Journal of Antimicrobial Agents 46 (2015) 603–609

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Review

Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and meta-analysis

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ABSTRACT

Colistin has been used to treat nosocomial pneumonia (NP) caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) via different administration routes. Whether patients may benefit from aerosolised colistin as adjunctive treatment was contradictory. We aimed to clarify the safety and efficacy of administering aerosolised and intravenous (IV-AS) colistin versus intravenous (IV) colistin alone in patients with NP caused by MDR-GNB. Two reviewers independently evaluated and extracted data from PubMed, EMBASE and Cochrane databases. Primary outcomes were clinical response rate, all-cause mortality (ICU or hospital), microbiological eradication and nephrotoxicity. Pooled odds ratios (ORs) were calculated and significance was determined by the *Z* test. Nine eligible studies involving 672 participants were included. The overall clinical response rate (improvement and cure) was significantly higher in the IV-AS group than that in the IV group [OR = 1.81, 95% confidence interval (CI) 1.30–2.53; *P* = 0.0005]. Patients treated with IV-AS colistin showed a higher rate of pathogen eradication (OR = 1.66, 95% CI 1.11–2.49; *P* = 0.01) and lower all-cause mortality compared with IV colistin (OR = 0.69, 95% CI 0.50–0.95; *P* = 0.02). Nephrotoxicity did not differ significantly between IV-AS and IV groups (five studies; 383 patients) (OR = 1.11, 95% CI 0.69–1.80; *P* = 0.67). These data indicate that IV-AS colistin has additional benefits compared with IV colistin alone. Clinicians should be encouraged to give combined administration routes in critically ill patients with NP caused by MDR-GNB.

İntravenöz kolistine ek olarak aerosol olarak verilmesi yararlıdır

Russell et al. BMC Pulmonary Medicine (2016) 16:40
DOI 10.1186/s12890-016-0202-8

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review

Christopher J. Russell[1,2*], Mark S. Shiroishi[3], Elizabeth Siantz[6], Brian W. Wu[4] and Cecilia M. Patino[5]

Abstract

Background: Ventilator-associated respiratory infections (tracheobronchitis, pneumonia) contribute significant morbidity and mortality to adults receiving care in intensive care units (ICU). Administration of broad-spectrum intravenous antibiotics, the current standard of care, may have systemic adverse effects. The efficacy of aerosolized antibiotics for treatment of ventilator-associated respiratory infections remains unclear. Our objective was to conduct a systematic review of the efficacy of aerosolized antibiotics in the treatment of ventilator-associated pneumonia (VAP) and tracheobronchitis (VAT), using the Cochrane Collaboration guidelines.

Methods: We conducted a search of three databases (PubMed, Web of Knowledge and the Cochrane Collaboration) for randomized, controlled trials studying the use of nebulized antibiotics in VAP and VAT that measured clinical cure (e.g., change in Clinical Pulmonary Infection Score) as an outcome measurement. We augmented the electronic searches with hand searches of the references for any narrative review articles as well as any article included in the systematic review. Included studies were examined for risk of bias using the Cochrane Handbook's "Risk of Bias" assessment tool.

Results: Six studies met full inclusion criteria. For the systemic review's primary outcome (clinical cure), two studies found clinically and statistically significant improvements in measures of VAP cure while four found no statistically significant difference in measurements of cure. No studies found inferiority of aerosolized antibiotics. The included studies had various degrees of biases, particularly in the performance and detection bias domains. Given that outcome measures of clinical cure were not uniform, we were unable to conduct a meta-analysis.

Conclusions: There is insufficient evidence for the use of inhaled antibiotic therapy as primary or adjuvant treatment of VAP or VAT. Additional, better-powered randomized-controlled trials are needed to assess the efficacy of inhaled antibiotic therapy for VAP and VAT.

Keywords: Antibiotics, Inhaled, Antibiotics, Aerosolized, Ventilator-associated pneumonia, Therapy

Aerosol olarak verilmesinin önerilmesi için yeterli kanıt yoktur

Journal of Infection ■■ (2018) ■■–■■

Contents lists available at ScienceDirect

Journal of Infection

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

Review

Intravenous plus inhaled versus intravenous colistin monotherapy for lower respiratory tract infections: A systematic review and meta-analysis

Konstantinos Z. Vardakas [a,b], Andreas D. Mavroudis [c], Maria Georgiou [a], Matthew E. Falagas [a,b,d,*]

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[b] *Department of Medicine, Henry Dunant Hospital Center, Athens, Greece*
[c] *Hellenic Police Health Headquarters, Athens, Greece*
[d] *Department of Medicine, Tufts University School of Medicine, Boston, MA, USA*

Kolistin: IV + İnhalasyon

- 13 çalışma(11 retrospektif, 2 prospektif)
- Veri kalitesi: Çok düşük – Düşük
- Dozlar farklı
- Düşük doz IV kolistin(< 6 MU) verilen çalışmalarda kombinasyon alanlara göre mortalite yüksek

Vardakas KZ et al. J Infect 2018

Study or Subgroup	Inhaled/Intravenous Events	Total	Intravenous Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 inhaled						
Amin et al. 2013	8	28	5	12	2.6%	0.69 [0.28, 1.67]
Bogovic et al. 2014	6	8	17	23	8.4%	1.01 [0.64, 1.62]
Demirdal et al 2016	23	43	38	80	12.7%	1.13 [0.78, 1.62]
Doshi et al 2013	16	44	27	51	8.4%	0.69 [0.43, 1.10]
Falagas et al. 2006	2	9	2	18	0.7%	2.00 [0.33, 11.97]
Ganapathy et al 2009	10	17	2	6	1.5%	1.76 [0.53, 5.86]
Kalin et al. 2012	16	29	7	15	5.0%	1.18 [0.63, 2.23]
Kofteridis et al 2010	10	43	18	43	4.8%	0.56 [0.29, 1.06]
Korbila et al 2010	31	78	19	43	9.6%	0.90 [0.58, 1.39]
Korkmaz et al. 2016	45	69	128	210	26.2%	1.07 [0.87, 1.31]
Naesens et al 2011	3	9	5	5	2.7%	0.38 [0.16, 0.92]
Perez-Pedrero et al. 2010	2	10	5	14	1.1%	0.56 [0.13, 2.33]
Tumbarello et al. 2013	45	104	48	104	16.4%	0.94 [0.69, 1.27]
Subtotal (95% CI)		**491**		**624**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	217		321			
Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 12 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**491**		**624**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	217		321			
Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 12 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Not applicable						

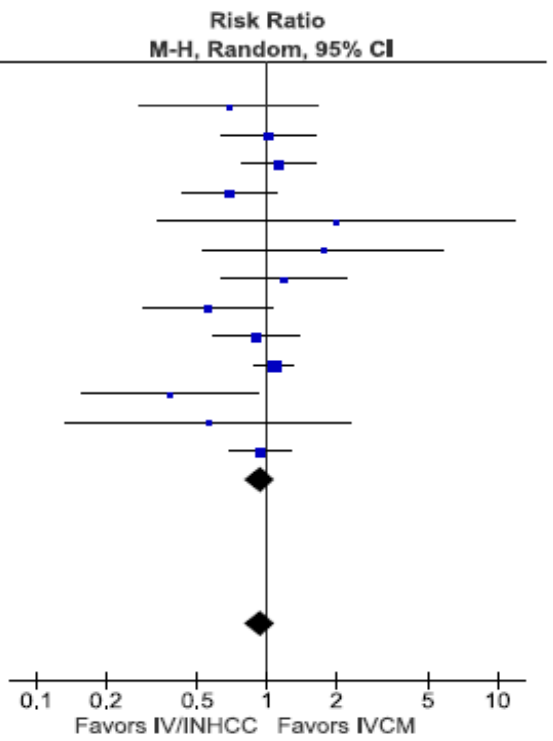


Fig. 2. Forest plot depicting the risk ratios (RR) of mortality among patients treated with IV/INHCC and IVCM. *(Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI. The areas of squares are proportional to the weight given to each study. Risk ratios are the centers of each square).*

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.

Rello J[1], Solé-Lleonart C[2], Rouby JJ[3], Chastre J[4], Blot S[5], Poulakou G[6], Luyt CE[3], Riera J[7], Palmer LB[8], Pereira JM[9], Felton T[10], Dhanani J[11], Bassetti M[12], Welte T[13], Roberts JA[11].

Overall, the panel recommends avoiding the use of nebulized antibiotics in clinical practice, due to a weak level of evidence of their efficacy and the high potential for underestimated risks of adverse events (particularly, respiratory complications).

Clin Microbiol Infect 2017

PHARMACOTHERAPY

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Brian T. Tsuji,[1,*,‡] Jason M. Pogue,[2,‡] Alexandre P. Zavascki,[3,4] Mical Paul,[5,6] George L. Daikos,[7] Alan Forrest,[8] Daniele R. Giacobbe,[9,10] Claudio Viscoli,[9,10] Helen Giamarellou,[11] Ilias Karaiskos,[11] Donald Kaye,[12] Johan W. Mouton,[13] Vincent H. Tam,[14] Visanu Thamlikitkul,[15] Richard G. Wunderink,[16] Jian Li,[17,§] Roger L. Nation,[18,§] and Keith S. Kaye[19,*,§]

(Pharmacotherapy 2019;39(1):10–39) doi: 10.1002/phar.2209

XIX. Should Inhaled Polymyxins Be Administered to Patients with HAP/VAP, and If So, Which Agent Is Preferred?

Recommendations. **R33**: We recommend that patients requiring IV polymyxin therapy for suspected or documented XDR gram-negative HAP or VAP should receive adjunctive polymyxin aerosol therapy (*Weak recommendation, low-quality evidence*).

R34: We recommend that for polymyxin aerosol therapy, either colistin or polymyxin B is appropriate (*Weak recommendation; very low-quality evidence*).

Pseudomonas aeruginosa

- VIM, IMP-1

  Özgümüş OB et al. Microb Drug Resist 2007

- VIM-2

  Yakupoğulları Y et al. J Antimicrob Chemother 2007

- VIM-5

  Bahar G et al. J Antimicrob Chemother 2004

P. aeruginosa - Direnç Gelişimi İn vivo

- 2006-2008 yılları arasında 850 YB hastası
- 172(%20) *P.aeruginosa*
- 53(%6.2) hastada en az 2 örnek pozitif - aynı klona ait
- 53 hastanın 17(%32)'sinde ilk izolat(A) ile ikinci izolat(B) arasında ≥4 kat MİK artışı mevcut
- 17 çift izolat genetik olarak farklı

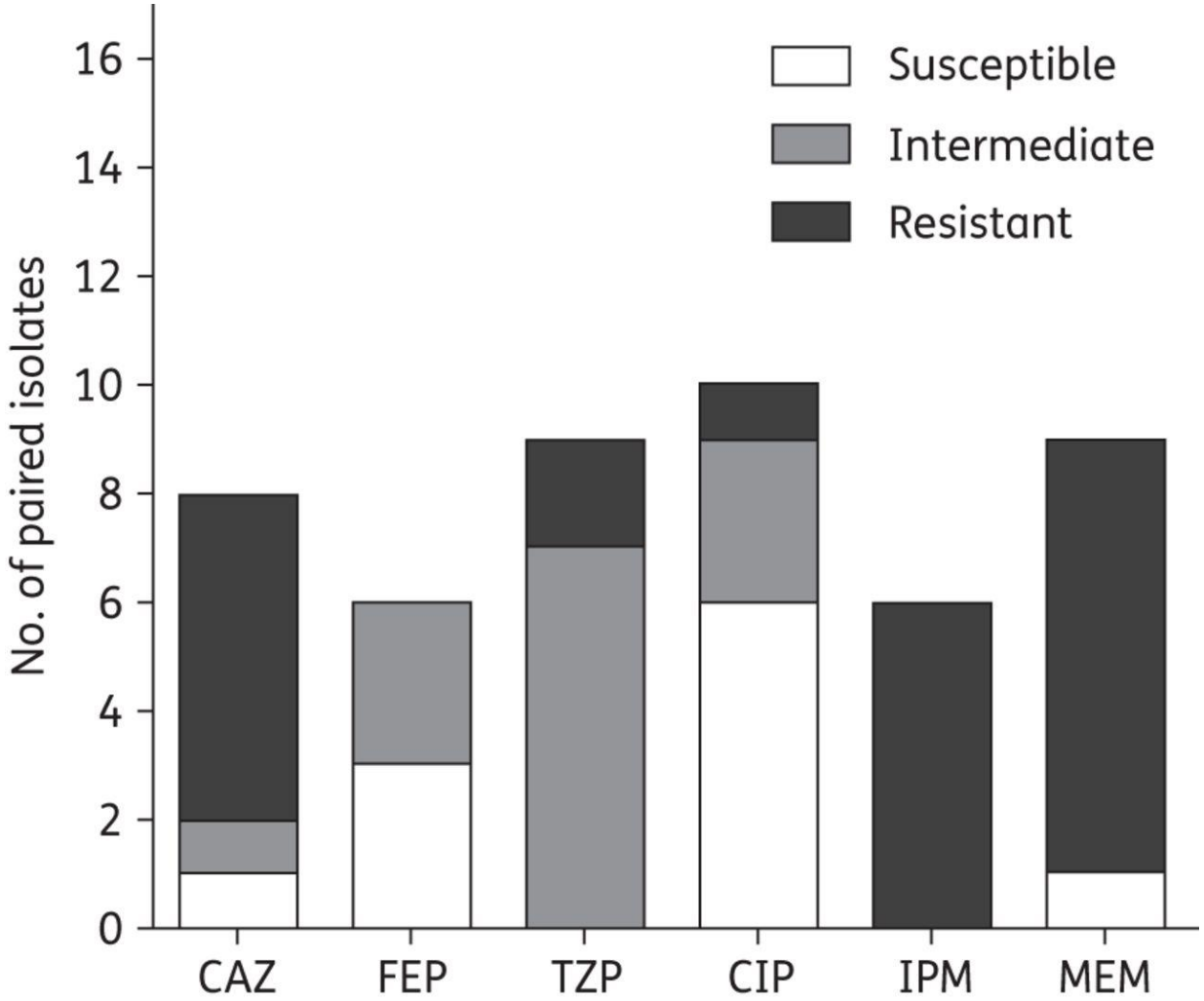
Sole M et al. J Antimicrob Chemother 2015

P. aeruginosa - Direnç Gelişimi İn vivo

- İmipenem MİK değerine göre 6 izolatta A ve B izolatları arasında 4-16 kat MİK artışı
- MİK artışı ≥4 kat:
  - -Seftazidim 8 izolat
  - -Sefepim 6 izolat
  - -Pip/Taz 9 izolat
  - -Sipro 10 izolat
- Direnç mekanizmaları: OprD, MexB, ampC

Sole M et al. J Antimicrob Chemother 2015

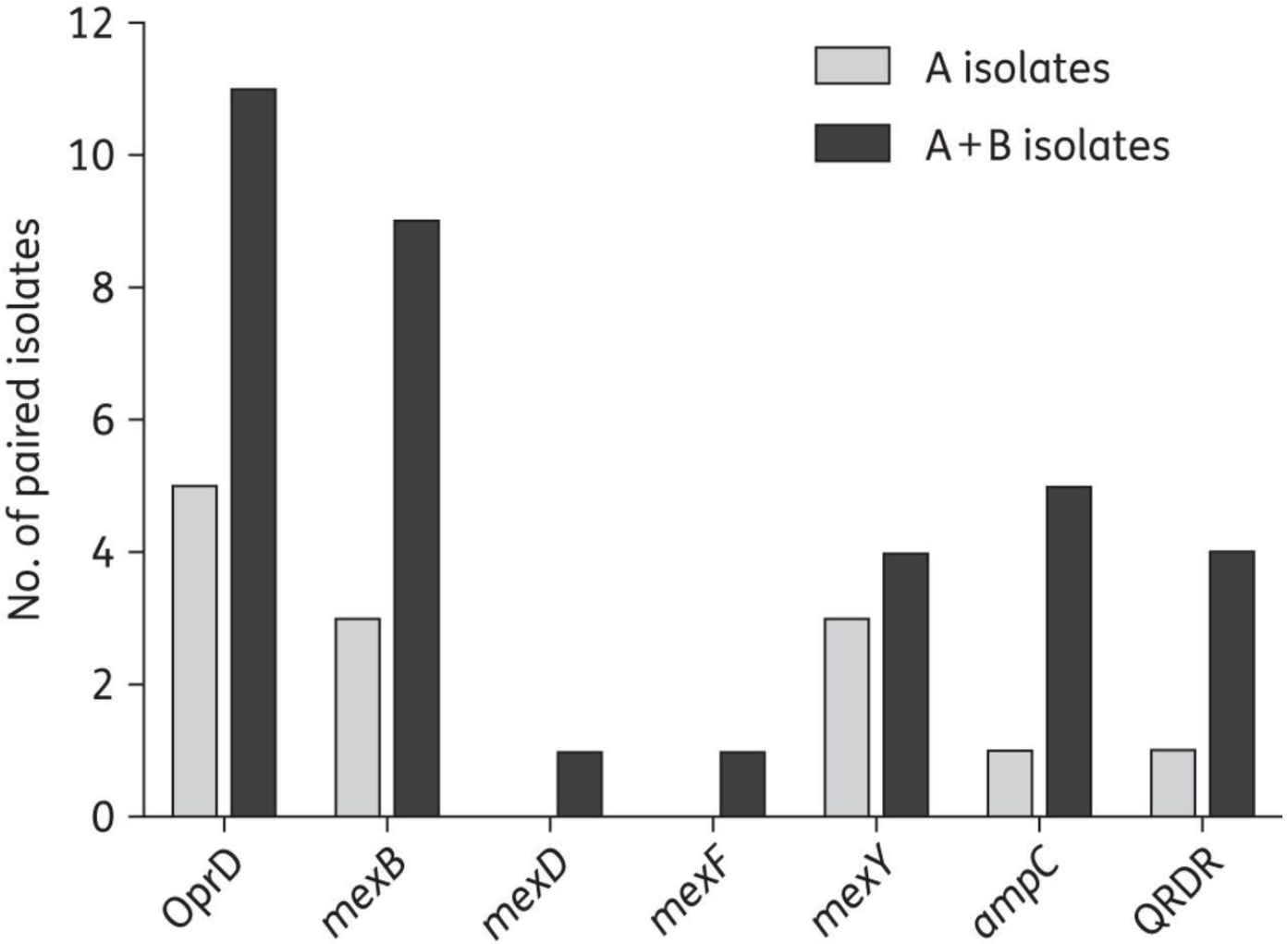
Number of B isolates showing increased MICs of the specific compounds compared with A isolates.



Mar Solé et al. J. Antimicrob. Chemother. 2015;70:3004-3013

Journal of Antimicrobial Chemotherapy

Analysis of the mechanisms of resistance acquired by the A and B isolates.



Mar Solé et al. J. Antimicrob. Chemother. 2015;70:3004-3013

Journal of Antimicrobial Chemotherapy

P. aeruginosa - Direnç Gelişimi İn vivo

- Çoklu direnç gelişimi için en riskli meropenem
- Seftazidim kendisine karşı direnç gelişimi açısından en riskli
- Pip/Tazo: Ekolojik etkileri daha az

Sole M et al. J Antimicrob Chemother 2015

- 47 çalışmanın alındığı meta-analiz(nötropenik hastalar)
- Kombinasyon ile monoterapi arasında ölüm oranları açısından fark yok(Pseudomonas enfeksiyonları için geçerli)
- Tedavi başarısızlığı: Aynı beta-laktam için fark yok, farklı beta-laktam için monoterapide daha az
- Tedavi başarısızlığı-ölüm oranları paralellik göstermiyor
- Bazı çalışmalarda ölüm oranları yok

Paul M et al. British Medical Journal 2003

- 64 çalışmanın alındığı meta-analiz(bağışıklığı kırılmamış hastalar)
- Gram negatiflerin neden olduğu sepsis olgularında kombinasyon ile monoterapi arasında fark yok
- Genel olarak kombinasyon rejimlerinde nefrotoksisite daha sık
- *P.aeruginosa*'nın neden olduğu sepsis için kombinasyon ile monoterapi arasında fark yok
- Çalışmaların kalitesi yeterli değil

Paul M et al. British Medical Journal 2004

- 17 gram negatif bakteriyemi çalışması
- Meta-analiz
- *P.aeruginosa* için kombinasyon yararlı

Safdar N et al. Lancet Infect Dis 2004

Pseudomonas aeruginosa

- 305 hasta(1997-2002) – *P. aeruginosa* bakteriyemisi
- 64 hastada mortalite(%21)
- Başlangıçtaki uygun tedavi mortaliteyi anlamlı olarak azaltıyor(%17.8-30.7,p=0.018)
- Kombinasyon tedavisi alanlarda başlangıç uygun antibiyotik tedavisi anlamlı olarak yüksek(%79.4-65.5,p=0.011)
- Kombinasyon öneriliyor

Micek ST et al. Antimicrob Agents Chemother 2005

Pseudomonas aeruginosa

- 593 bakteriyemi
- 30.gün mortalitesi
- Kombinasyon = Monoterapi

Pena C et al. Clin Infect Dis 2013

Çoklu Dirençli *P.aeruginosa* Tedavisi

- Kombinasyon(in vitro)

  Tikarsilin + Tobramisin + Rifampin
  Seftazidim veya sefepim + Kinolon
  Seftazidim + Kolistin
  Polimiksin B + Rifampin
  Polimiksin B + İmipenem
  Azitromisin + Tobramisin + Doksisiklin + TMP veya Rifampin

- Kombinasyon(klinik)

  Sefepim + Amikasin
  Polimiksin B + (karbapenem veya aminoglikozid veya kinolon veya beta-laktam)

Rahal JJ et al. Clin Infect Dis 2006

P.aeruginosa Enfeksiyonlarında Tedavi

- Ciddi enfeksiyonlar
  Beta-laktam + Aminoglikozid veya Kinolon
- Komplike Olmayan ÜSE
  Monoterapi

- Karbapenem dirençli(ÇİD)
  Kolistinli kombinasyon

McCarthy K et al. Semin Respir Crit Care Med 2015
Martis N et al. J Infect 2014

Çoklu Dirençli *P.aeruginosa* Tedavisi

- Karbapenem dirençli olgularda Seftolozan/Tazobaktam tedavisi

Munita JM et. Clin Infect Dis 2017

- Kolistin dirençli olgularda Seftolozan/Tazobaktam tedavisi

Alvarez Lerma A et al. Revista Espanola de Quimioterapia 2017

- Karbapenem dirençli VİP tedavisinde Kolistin + Meropenem(yüksek doz, uzamış infüzyon)

Sarda C et al. Expert Rev Respir Med 2019

PHARMACOTHERAPY accp

SPECIAL ARTICLE

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

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- Karbapenem-R *P.aeruginosa*
  -Kolistin + in vitro etkili 1 veya daha fazla AB
- Sadece kolistin duyarlı ise
  -Kolistin + en düşük MİK'e sahip 1 ve/veya 2 AB

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Özet-ÇİD *K.pneumoniae*

- Karbapenem dirençli *K pneumoniae* için Kolistin + Meropenem(yüksek doz, uzamış infüzyon ya da sürekli infüzyon)
- Karbapenem dirençli *K pneumoniae* için Kolistin + Fosfomisin veya AG veya tigesiklin
- Meropenem MİK'leri kombinasyonun içeriğini belirleyici
- Meropenem + Fosfomisin
- Seftazidim/Avibaktam

Özet- ÇİD *A.baumannii*

- Karbapenem dirençli *A baumannii* için meta-analizler ve randomize kontrollü bir çalışma kolistin monoterapisini destekliyor
- Meropenem + Kolistin
- Sulbaktam = Kolistin
- Meropenem + Kolistin = Meropenem + SAM
- Kolistin + Karbapenem = Kolistin + SAM

Özet - ÇİD *P.aeruginosa*

- Kolistin + Meropenem
- Seftolozan/Tazobaktam
- Karbapenem-R *P.aeruginosa*
  -Kolistin + in vitro etkili 1 veya daha fazla AB
- Sadece kolistin duyarlı ise
  -Kolistin + en düşük MİK'e sahip 1 ve/veya 2 AB

Özet

- Kolistin + Aminoglikozid kombinasyonundan kaçınalım(nefrotoksisite)
- Meropenem yüksek doz ve uzamış infüzyon
- Klavuzlardaki tigesiklin dozu ruhsatlı dozun 2 katı
- Fosfomisin tek başına kullanılmamalı
- Kolistin inhalasyon?
- Şu ana kadar olan kanıtların çoğu KPC(+) *Klebsiella pneumoniae* çalışmalarından

Özet

- Yeni antibiyotikler umut verici
- Enzim tipi
- Sinerji testleri
- İlaç düzeylerinin izlenmesi
- PK/PD