Karbapenem Dirençli Enterobacteriaceae ve Tedavisi

Prof. Dr. Halis Akalın

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

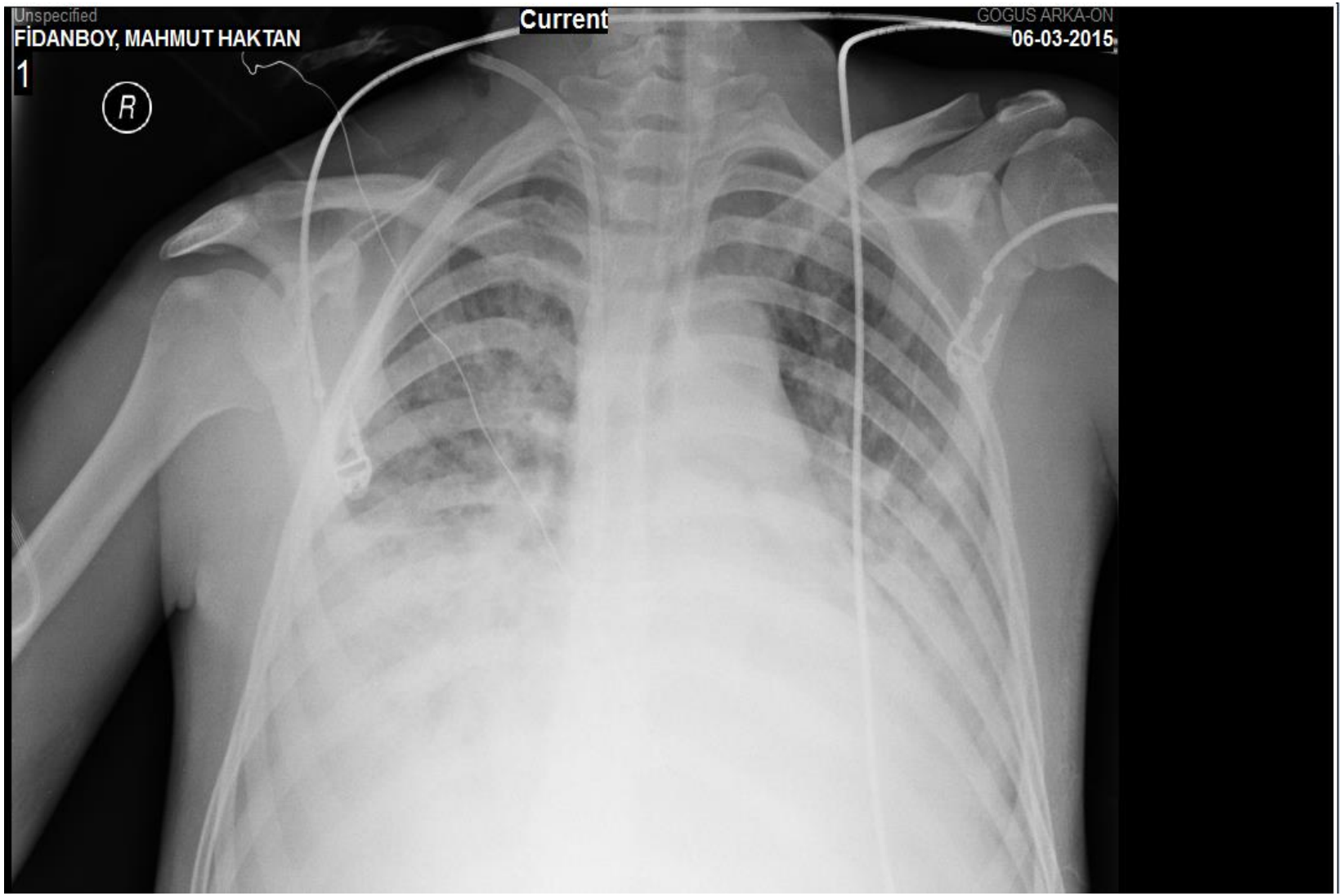
- Cilt ve skleralar ikterik
- Traube kapalı – Dalak 3 cm
- Lökosit 3337/mm^3
- Trombosit 107000/mm^3
- ALT 44 IU/L, AST 127 IU/L, TB 25 mg/dl, DB 15 mg/dl, INR 1.37
- CRP 1.2 mg/dl
- Batın USG(Dış Merkez): KC 154 mm, grade 2 hepatosteatoz, dalak 175 mm

- 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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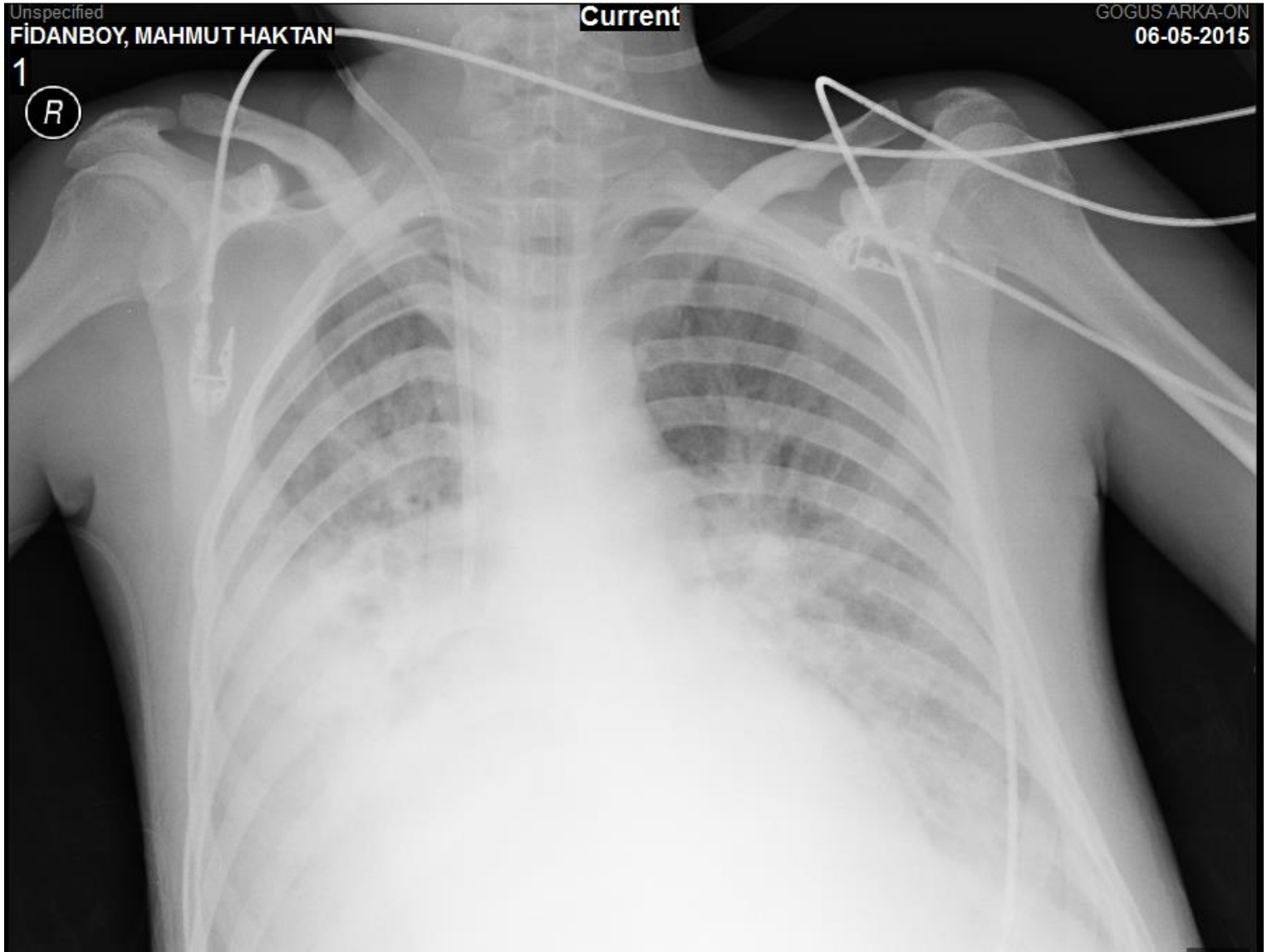
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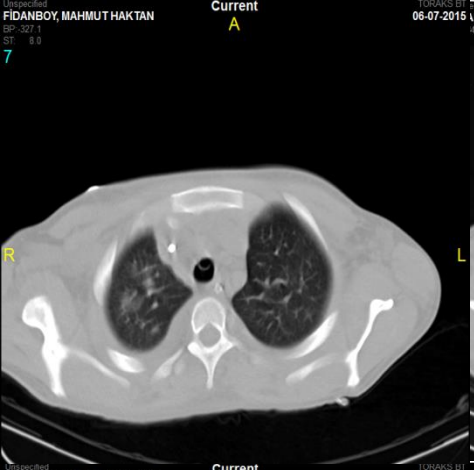
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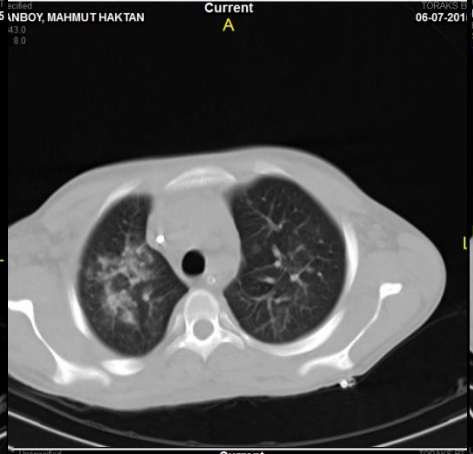
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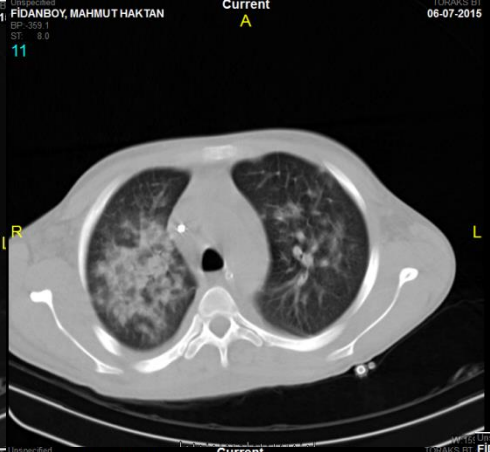
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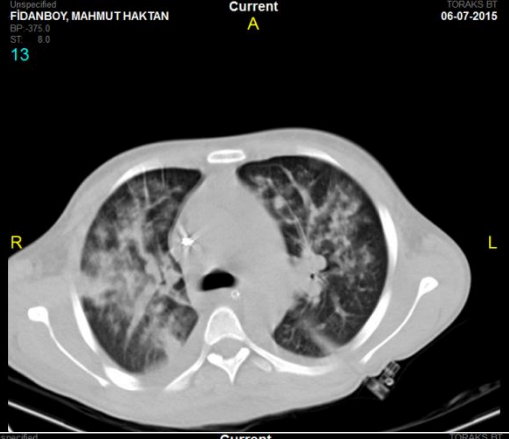
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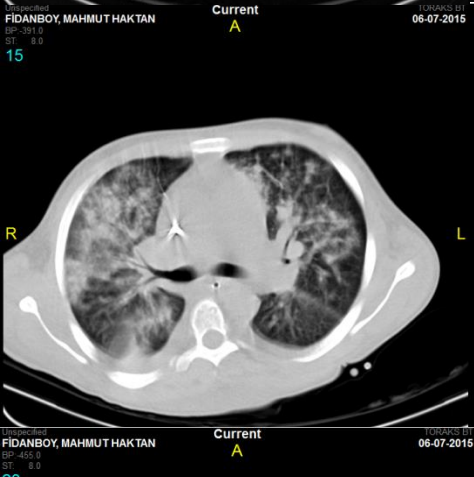
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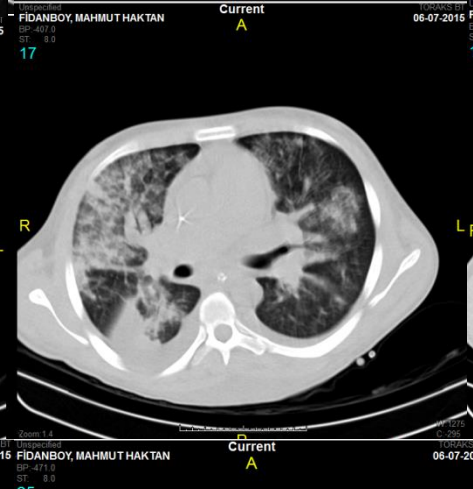
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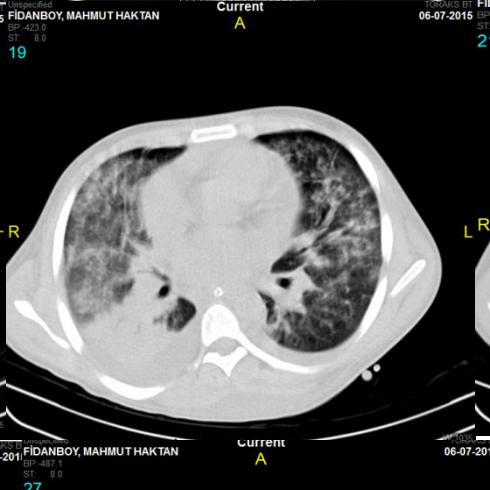
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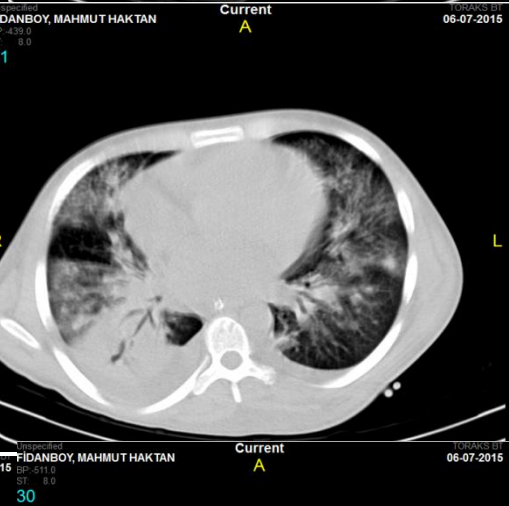
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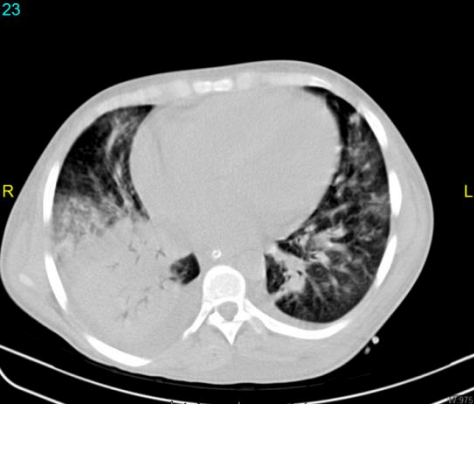
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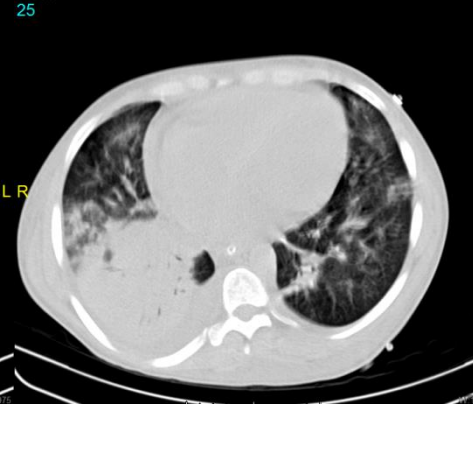
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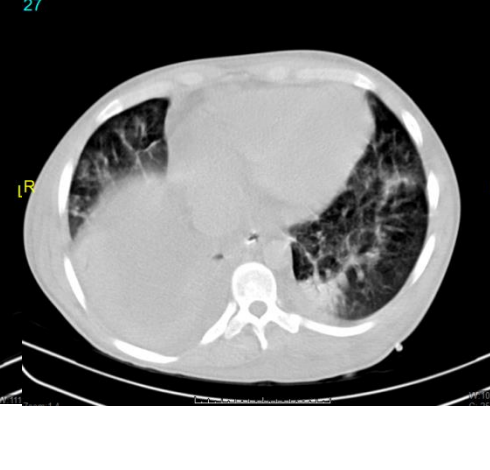
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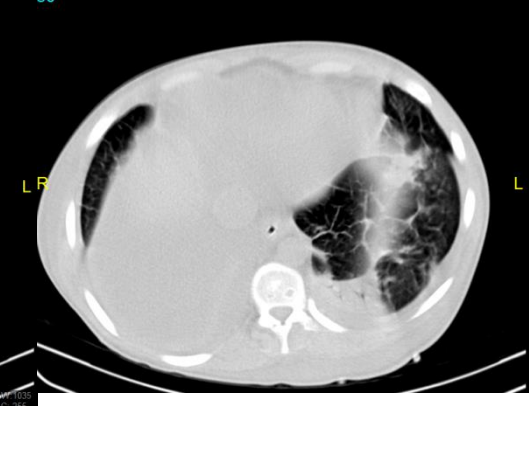
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R
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7/6/2015 Toraks BT

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			

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En olası enfeksiyon etkeni hangisi olabilir?

A-*Candida* spp.

B-*Klebsiella pneumoniae*

C-*Acinetobacter baumannii*

D-VRE

KD-*K.pneumoniae* Enfeksiyonu Risk Faktörleri

- Çukurova Üniv. Tıp Fak, 2012
- 47 KD ve 51 KS *K.pneumoniae* ile enfekte hasta
- Meropenem ve 3.KS kullanımı ile karbapenem direnci arasında ilişki(OR 3.244 ve OR 3.590)
- Bağımsız risk faktörleri:3.KS kullanımı, NG tüp kullanımı ve NŞ-YBÜ

Ulu AC et al. Med Sci Monit 2015

KD-Enterobacteriaceae

- 34 Merkez, 2013, İspanya
- Prospektif, 245 hasta
- %74 *K.pneumoniae*
- %74 OXA-48, %24 MBL, %2 KPC
- %67 Enfeksiyon-%33 Kolonizasyon
- ÜSE(%43), CYDE(%21)
- Enfeksiyonların %10'unda bakteriyemi

Palacios-Baena ZR et al. J Infect 2015

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

Sürveyans Kültürleri

- Entübasyonun ilk günü alınan kültürün değeri, 2 günde bir alınan sürveyans kültürlerine göre geç dönem pnömoni etkenini tahmin etmede daha düşük

  Gürsel G et al. Scand J Infect Dis 2010

- VİP tanısı öncesi ETA kültüründe *P.aeruginosa, A.baumannii* veya MRSA üremişse dikkate alınmalı

  Joseph NM et al. Int J Infect Dis 2010

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

- 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			

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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

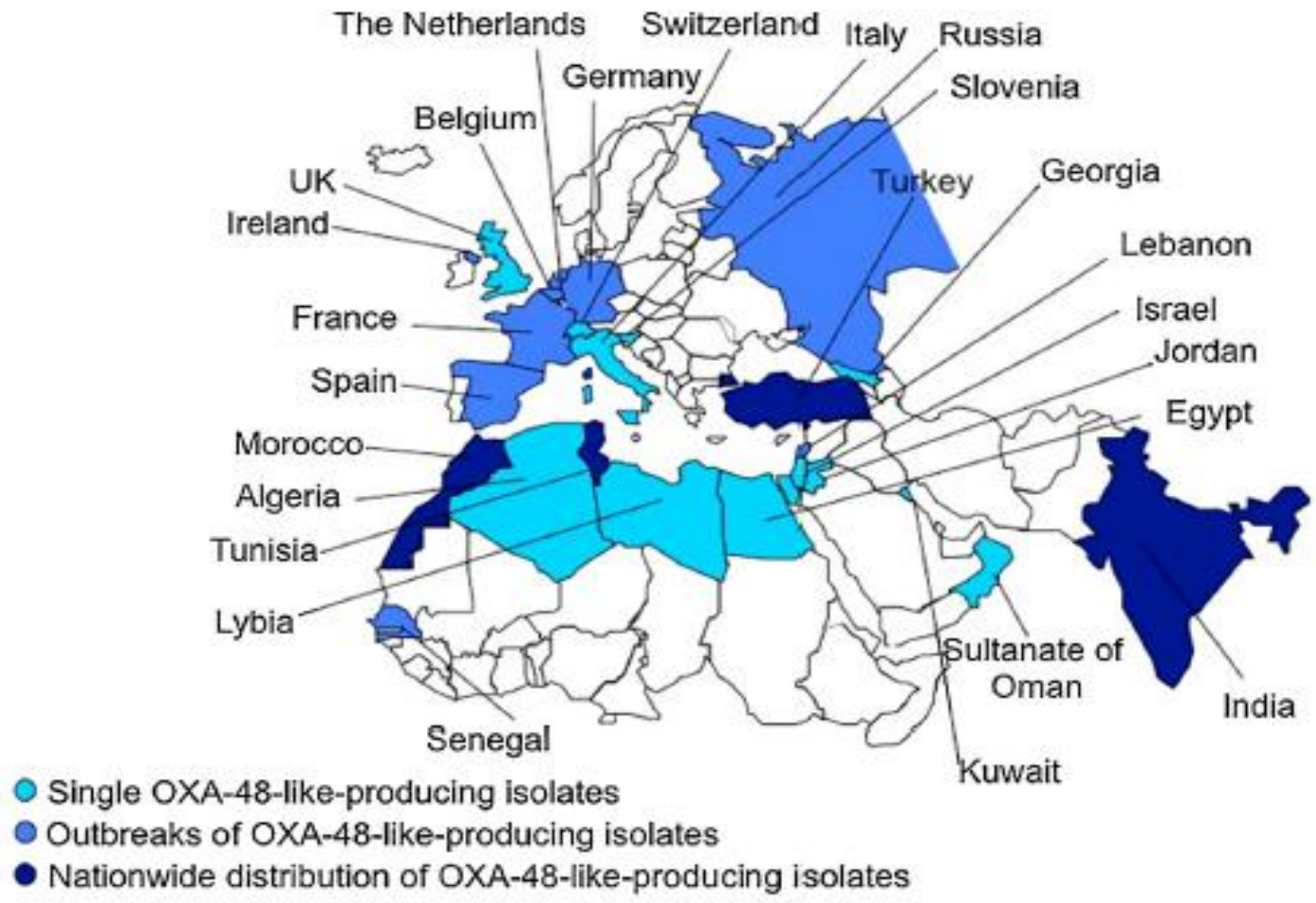

Fig. 2. Worldwide spread of OXA-48 producing strains.
Diffusion des souches OXA-48 dans le monde.

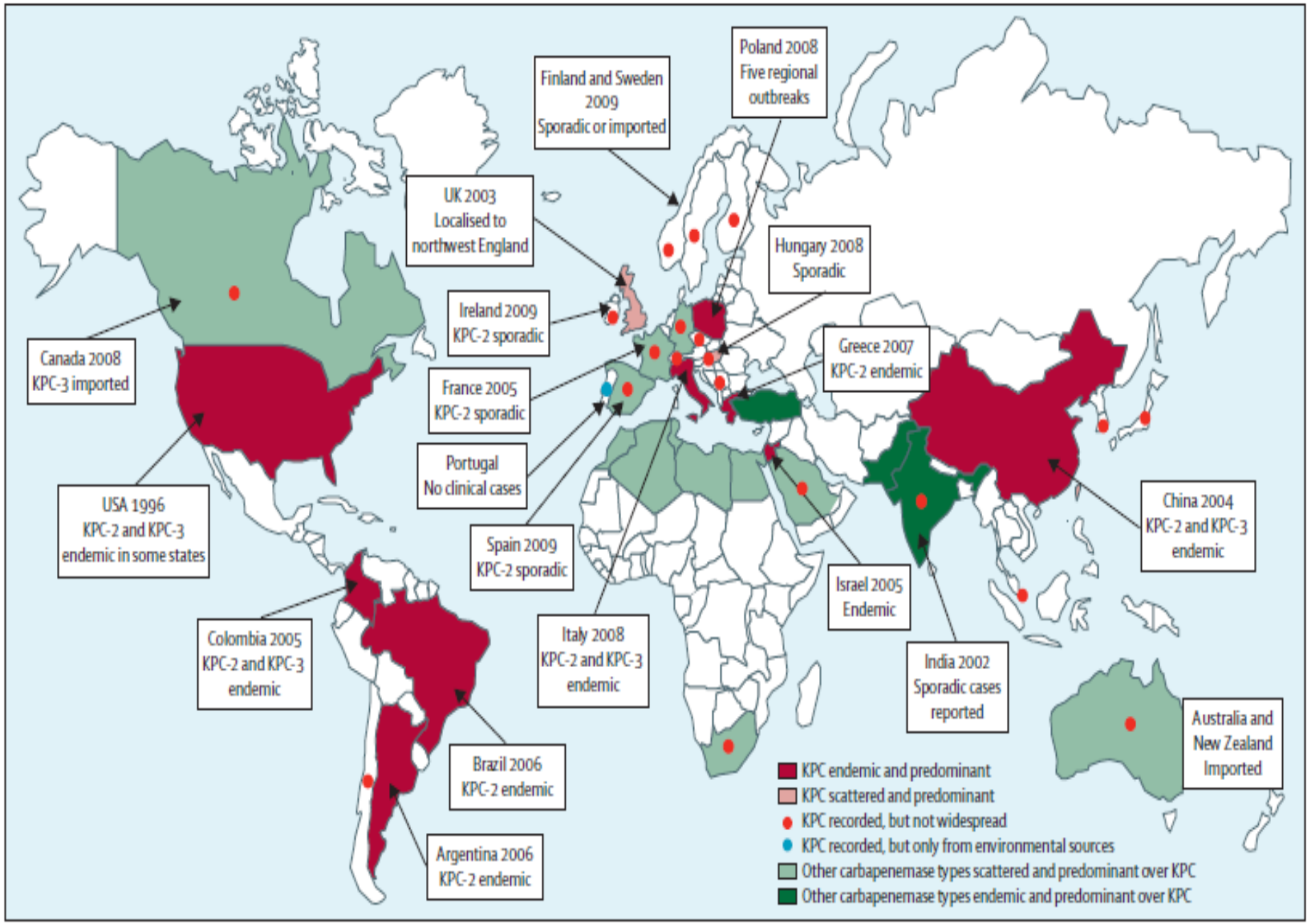

Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin

Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

Klebsiella pneumoniae

- OXA-48

  Carrer A et al. Antimicrob Agents Chemother 2008
  Aktaş Z et al. Chemother 2008

- VIM-1

  Yıldırım İ et al. J Chemother 2007

- OXA-48 + CTX-M + Dış membran protein kaybı

  Gülmez D et al. Int J Antimicrob Agents 2008

Klebsiella pneumoniae

- Romanya'dan gelen bir hastada KPC-2

  Labarca J et al. New Microbes New Infections 2014

- Bağdat'tan gelen bir hastada NDM-1

  Poirel L et al. Antimicrob Agents Chemother 2012

Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study

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Summary

Background Gaps in the diagnostic capacity and heterogeneity of national surveillance and reporting standards in Europe make it difficult to contain carbapenemase-producing Enterobacteriaceae. We report the development of a consistent sampling framework and the results of the first structured survey on the occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in European hospitals.

Lancet Infect Dis 2017; 17: 153–63
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	Hospitals submitting carbapenem non-susceptible *K pneumoniae* isolates (n)	Number of submitted carbapenem non-susceptible *K pneumoniae* isolates	Confirmed carbapenemase-producing *K pneumoniae* isolates					Other (n, %)*
			KPC (n, %)	NDM (n,%)	OXA-48-like (n, %)	VIM (n, %)	Total (n, %)	
Albania	3	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)
Austria	6	15	6 (40·0)	2 (13·3)	2 (13·3)	0 (0)	10 (66·7)	5 (33·3)
Belgium	11	48	13 (27·1)	2 (4·2)	18 (37·5)	0 (0)	33 (68·8)	15 (31·3)
Bulgaria	3	4	0 (0)	2 (50·0)	0 (0)	0 (0)	2 (50·0)	2 (50·0)
Turkey	17	124	0 (0)	9 (7·3)	98 (79·0)	5 (4·0)	112 (90·3)	12 (9·7)
UK-England and Northern Ireland	15	47	14 (29·8)	3 (6·4)	7 (14·9)	1 (2·1)	25 (53·2)	22 (46·8)
UK-Scotland	4	8	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (100)

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

Aslı ÇAKAR[1], Yakut AKYÖN[1], Deniz GÜR[1], Onur KARATUNA[2], Dilara ÖĞÜNÇ[3], Betil ÖZHAK BAYSAN[3] Nilay ÇÖPLÜ[4], Mustafa ÇAĞATAY[4], Abdullah KILIÇ[5], Mehmet BAYSALLAR[5], Zahir BAKICI[6], Cem ÇELİK[6], Zeynep GÜLAY[7], Şöhret AYDEMİR[8], Alper TÜNGER[8], Hüseyin KILIÇ[9], Barış Derya ERÇAL[9], Zulal AŞÇI TORAMAN[10], Yasemin ZER[11], Ayşe BÜYÜKTAŞ[11], Selma AY[12], Zerrin AKTAŞ[13], Çiğdem KAYACAN[13], Gülçin BAYRAMOĞLU[14], Faruk AYDIN[14], Devrim DÜNDAR[15], Ufuk HASDEMİR[16], Ramazan AYAŞ[16], Keramettin YANIK[17], Murat GÜNAYDIN[17], Hüseyin GÜDÜCÜOĞLU[18], Mehmet PARLAK[18]

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)

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].

TABLE 1

Enzymes conferring carbapenem resistance in Enterobacteriaceae

Enzyme	Common genetic platform	Species distribution in Enterobacteriaceae	Geographic distribution
KPC (*Klebsiella pneumoniae* carbapenemase)	*K pneumoniae* sequence type 258, various plasmids types, transposon Tn*4401*x	*K pneumoniae*, *Escherichia coli*, *Enterobacter* species, diverse Enterobacteriaceae	Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America
NDM (New Delhi metallo-beta-lactamase)	Various plasmid types	*K pneumoniae* and *E coli* predominantly, diverse Enterobacteriaceae	Indian subcontinent and the Balkan region, and around the world
OXA-48 (oxacillinase)	IncI/M-type plasmid	*K pneumoniae* predominantly, diverse Enterobacteriaceae	Southern and Western Europe, Turkey and North Africa; rare in the United States
VIM (Verona integron-encoded metallo-beta-lactamase)	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in Italy, Greece, and the Far East, sporadic globally
IMP	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in the Far East and South America, sporadic globally
SME	Chromosome	*Serratia marcescens*	Sporadic in North America and South America

BASED ON INFORMATION IN TZOUVELEKIS LS, MARKOGIANNAKIS A, PSICHOGIOU M, TASSIOS PT, DAIKOS GL. CARBAPENEMASES IN *KLEBSIELLA PNEUMONIAE* AND OTHER ENTEROBACTERIACEAE: AN EVOLVING CRISIS OF GLOBAL DIMENSIONS. CLIN MICROBIOL REV 2012; 25):682–707.

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

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

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

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

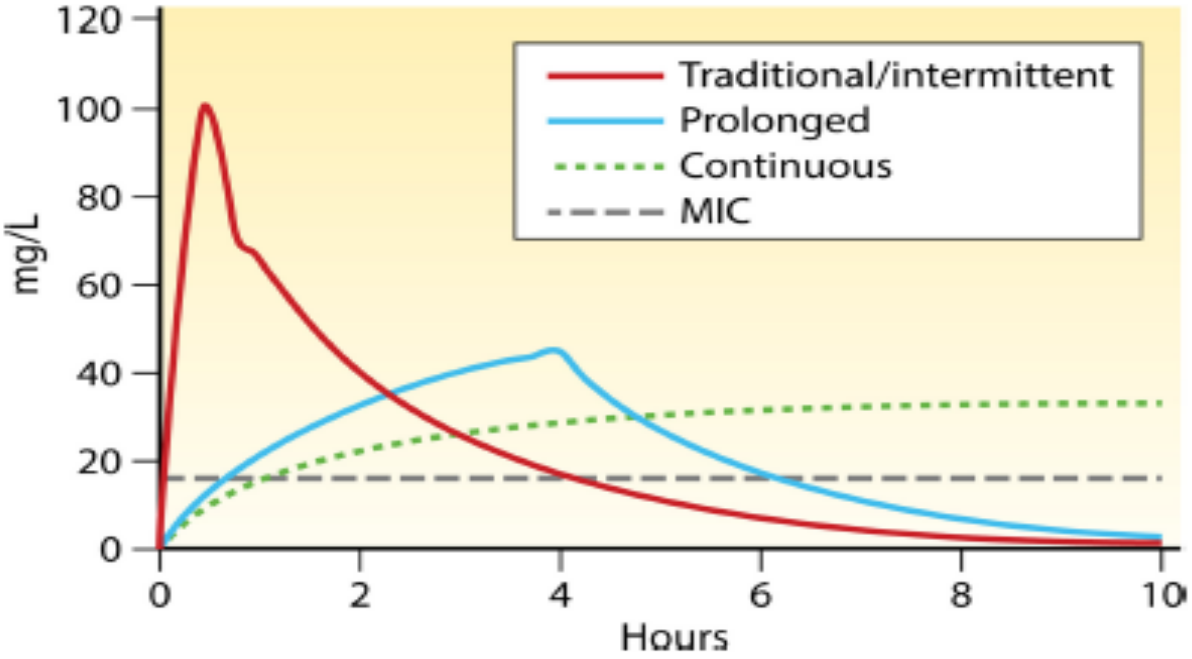

FIG 1 Schematic plot demonstrating the effects of prolonged and continuous beta-lactam infusion dosing regimens on the concentration-time curve and time above an MIC, compared with traditional intermittent infusion.

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]

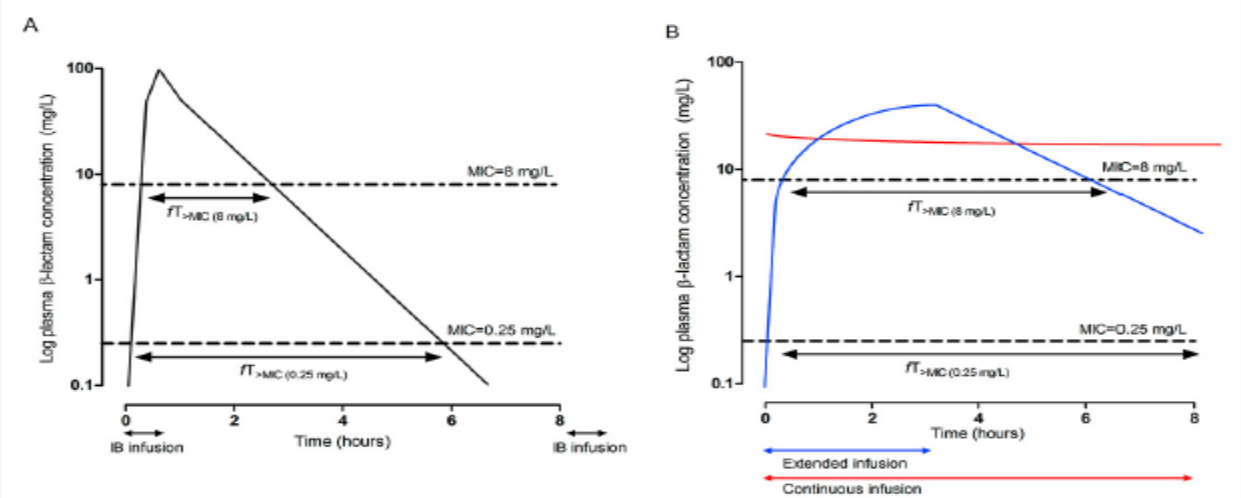

Figure 1

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

- 25 YBÜ, ÇM çalışma(BLING-II)
- Pip/Tazo, Tik/Klav, Meropenem
- 432 ağır sepsisli hasta
- Sürekli infüzyonda aralıklı infüzyona göre:
  -28.günde YBÜ de yatış günleri aynı
  -Klinik iyileşmede fark yok(p=0.56)
  -90.gündeki mortalitede fark yok(p=0.61)

Dulhunty JM et al. Am J Respir Crit Care Med 2015

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

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

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

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

J Antimicrob Chemother 2015; **70**: 905–913
doi:10.1093/jac/dku432 Advance Access publication 25 October 2014

Journal of Antimicrobial Chemotherapy

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

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Received 24 June 2014; returned 4 August 2014; revised 11 September 2014; accepted 29 September 2014

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

Table 2. Potential Treatment Algorithm for Carbapenem-Resistant KPC-Producing *Klebsiella pneumoniae

Infection Source	Empiric Treatment: Core Drugs	Empiric Treatment: Possible Adjunct Drugs	Antimicrobial Susceptibility Directed Treatment Considerations
Bloodstream	• High-dose meropenem or doripenem • And polymyxin B	• Aminoglycoside • Tigecycline • Fosfomycin • Rifampin	Meropenem/doripenem: • MIC ≤16 µg/mL continue high-dose meropenem/ doripenem • MIC >16 µg/mL consider alternative in vitro active antimicrobial[a] Polymyxin B/colistin: • MIC ≤ 2 µg/mL continue polymyxin B/colistin[b,c] • MIC >2 µg/mL consider alternative in vitro active antimicrobial If both meropenem/doripenem MIC (>16 µg/mL) and polymyxin B/colistin MIC (>2 µg/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen[d,e] If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen[e] Tigecycline: • MIC ≤1 µg/mL consider tigecycline[d] • MIC >1 µg/mL consider alternative in vitro active antimicrobial Fosfomycin[f]: • MIC ≤32 µg/mL consider fosfomycin • MIC >32 µg/mL consider alternative in vitro active antimicrobial Amioglycoside: • MIC ≤2 µg/mL (Gentamicin/ Tobramycin) or ≤4 µg/mL (Amikacin) consider aminoglycoside • MIC >2 (Gentamicin/ Tobramycin) or >4 µg/mL (Amikacin) consider alternative in vitro active antimicrobial
Lung	• High-dose meropenem or doripenem • And polymyxin B	• Tigecycline • Aminoglycoside • Fosfomycin • Rifampin	
Gastrointestinal/ biliary tract	• High-dose meropenem or doripenem • And polymyxin B • And high-dose tigecycline	• Fosfomycin • Rifampin	
Urine	• High-dose meropenem or doripenem • And fosfomycin[g] • Or aminoglycoside[g]	• Colistin • Aminoglycoside	

Abbreviations: CRE, carbapenem-resistant enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; OXA, oxacillinase.

*CRE infections are complicated and associated with high mortality; always consult a local infectious diseases expert in the management of serious CRE infections and always base treatment on antimicrobial susceptibility results. If the pathogen is suspected to be a MBL or OXA-48, aztreonam may be a preferred empiric core drug. If aztreonam MIC ≤8 µg/mL, consider continuing aztreonam at a dose of 6 to 8 g/day split into 3–4 doses that are given as 3–4 hours infusion. For patients who are critically ill or with deep-seated infections, consider empiric and antibiogram-directed combination therapy with 3 drugs. There are limited clinical data supporting the use of aminoglycosides, rifampin, and fosfomycin. If any of these drugs have in vitro activity and are selected for use (especially for infections outside the urinary tract for aminoglycosides and fosfomycin), consider use in combination with 2 other in vitro active drugs due the potential for the emergence of on-treatment resistance.

[a] Pharmacokinetic data have found that high-dosed, prolonged infusion meropenem has a high probability of target attainment up to an MIC of 16 µg/mL. However, mortality may be higher with meropenem MICs ≥8 µg/mL. Strongly consider combination therapy with moderately elevated (≥4 µg/mL) to elevated (≥8–16 µg/mL) meropenem MICs.

[b] May be difficult to achieve adequate plasma concentrations of polymyxin B/colistin with a polymyxin B/colistin MIC of 1–2 µg/mL.

[c] There are several challenges associated with polymyxin B/colistin MIC testing (see refs. [77, 78] for more information).

[d] High-dose tigecycline should always be considered if a tigecycline-based regimen is used. If tigecycline is used as an adjunct drug, consider the tigecycline MIC and risks and benefits of using high dosing vs traditional dosing.

[e] Dual carbapenem-based regimen should include high-dose meropenem or high-dose doripenem and ertapenem 1 gm daily, and it may be most effective in combination with a third drug.

[f] Oral fosfomycin should not be used for management of infections outside the urinary tract. Intravenous fosfomycin is not available in the United States. See text and Table 3 for more information on fosfomycin treatment.

[g] Urinary tract infections in noncritically ill patients may be successfully treated with monotherapy with in vitro active fosfomycin or an aminoglycoside. However, combination therapy may still be warranted due to the potential for the emergence of resistance. In critically ill patients, strongly consider combination therapy.

Morrill HJ et al. Open Forum Infect Dis 2015

Tedavi değişikliğini nasıl yaparsınız?

A-Mevcut tedaviye devam ederim

B-Tigesiklin eklerim

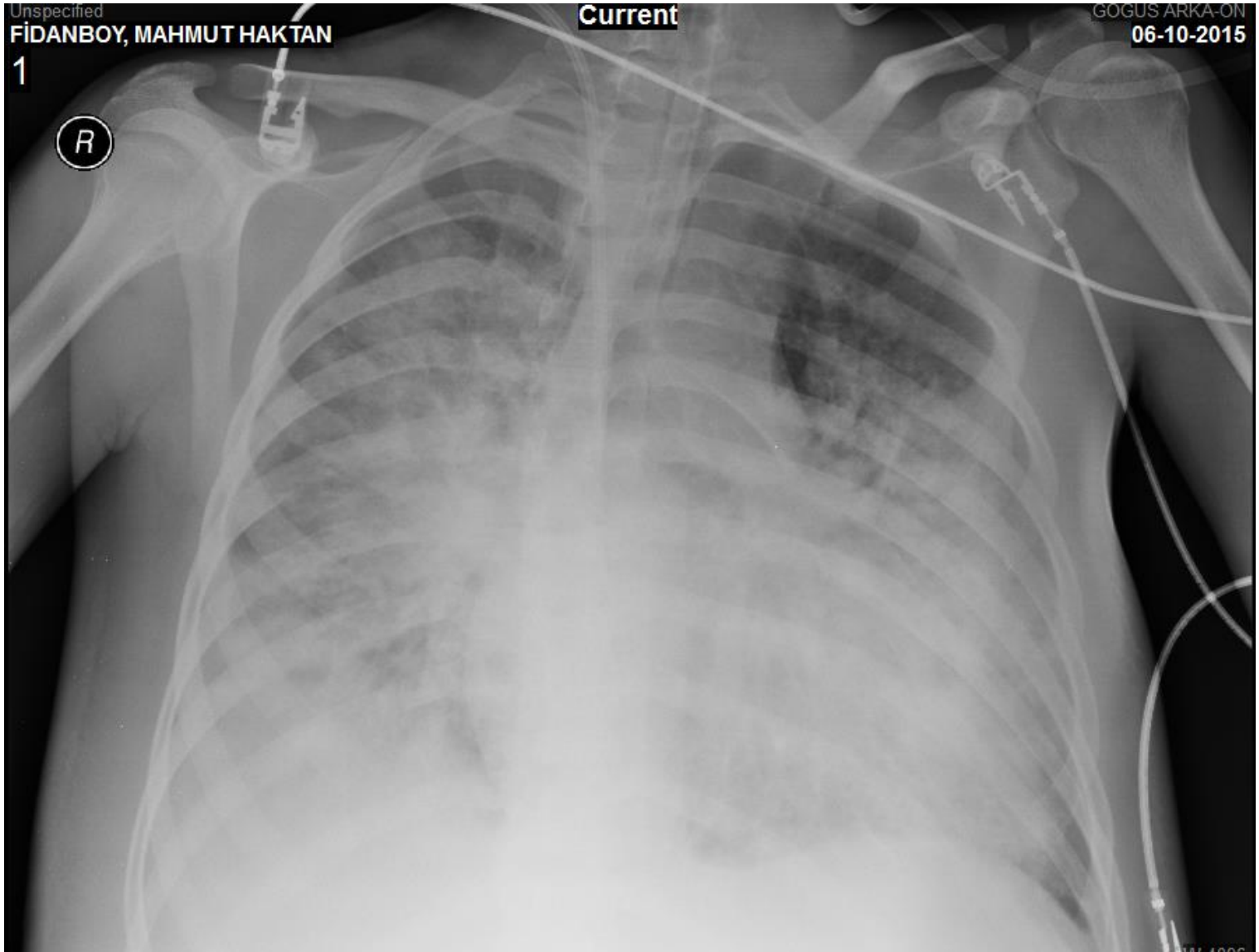
C-Kolistine devam ederim. Meropenemi uzamış infüzyon şeklinde veririm

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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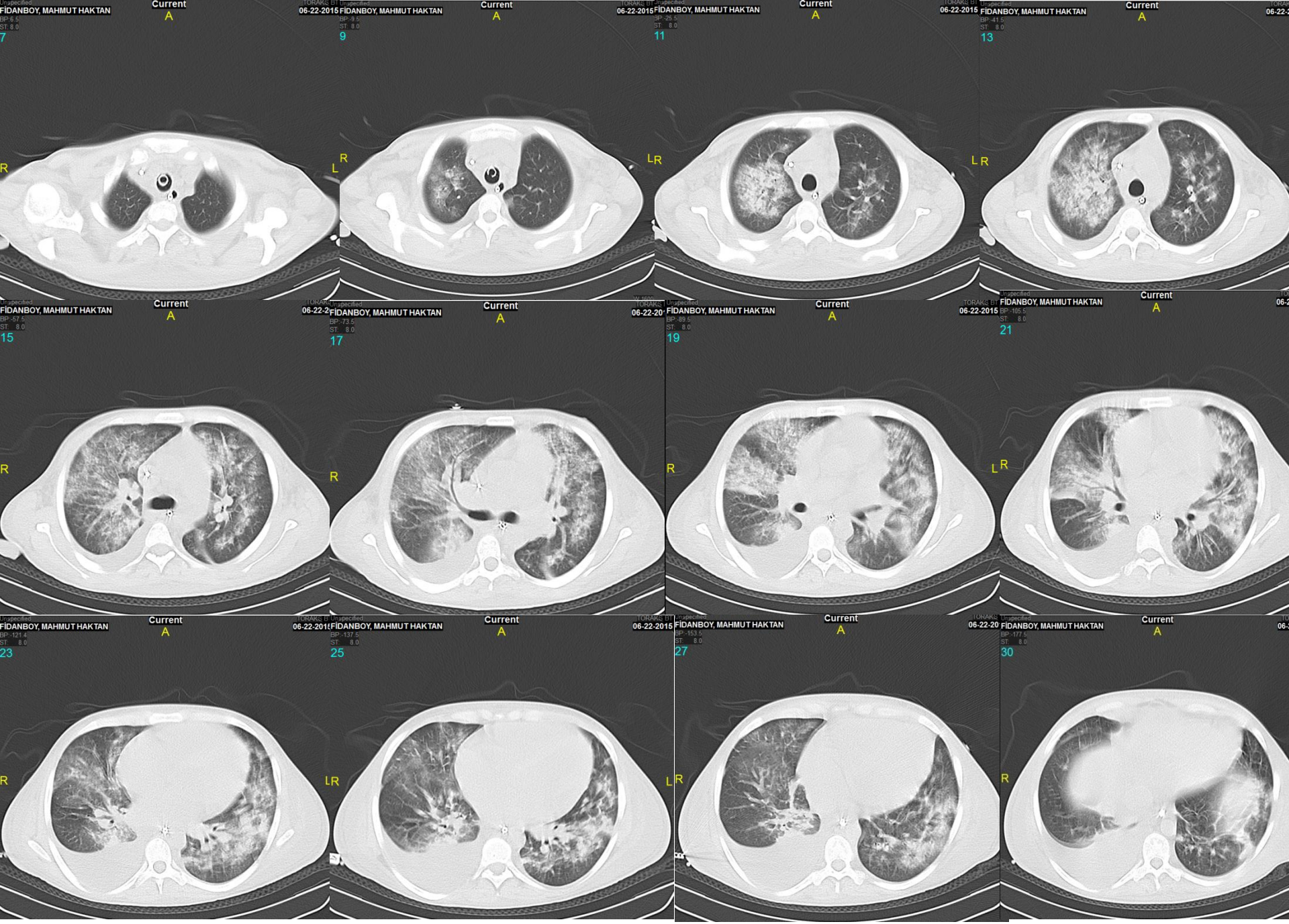
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- 1.Her iki akciğerde izlenen periferik akciğerin kısmen korunduğu keskin sınırlı birleşmeye meyilli irregüler yoğunluk artımları plevral sıvı ve cilt altı dokulardaki dansite artışı ile birlikte değerlendirildiğinde pulmoner ödem lehine değerlendirilmektedir. 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

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.

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.

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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 (≥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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Bactericidal effect

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

KPC(+) *K. pneumoniae* - Fosfomisin

- 11 erişkin hasta
- Bakteriyemi, VİP, ÜSE, CAE
- Fosfomisin 4x4 g IV
- Renal yetm veya >70 yaş 4x2 g IV
- Kombinasyon(Kolistin 6, Genta 3, Pip/Tazo1)
- Hastane içi mortalite %18.2

Michapoulos A et al. Clin Microbiol Infect 2010

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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.

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.

Table 7
Description of safety population ($n = 66$) and reported adverse events (AEs).

Duration of fosfomycin administration [median (IQR)]	12 (7–15)
Severe hypokalaemia [n (%)]	10 (15.2)
Lowest K^+ value (mEquiv./L) (mean ± S.D.)	2.7 ± 0.3
Renal toxicity [n (%)]	3 (4.5)
Thrombocytopenia [n (%)]	4 (6.1)
Diarrhoea/CDI [n (%)]	2 (3.0)
Rash [n (%)]	1 (1.5)
Neutropenia [n (%)]	1 (1.5)
Withdrawal of fosfomycin treatment owing to AEs [n (%)]	4 (6.1)[a]

IQR, interquartile range; S.D., standard deviation; CDI, *Clostridium difficile* infection.
[a] One case each of severe hypokalaemia on the 18th day of therapy, rash on the 15th day, *C. difficile* diarrhoea on the 14th day and neutropenia on the 18th day (white blood cell count 1900 cells/mm^3).

Retrospective analysis of fosfomycin combinational therapy for sepsis caused by carbapenem-resistant *Klebsiella pneumoniae*

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Abstract. The aim of the present study was to compare the efficacy and safety of fosfomycin combinational therapy with other antibiotics for the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP). This retrospective cohort study examined 104 cases of sepsis caused by CRKP occurring between January 2012 and November 2014 in Shanghai Tenth People's Hospital. Three categories of patient outcome were assessed: Survival/mortality, duration of intensive care unit stays and duration of medical ventilation. Univariate ordinal analyses were adopted to evaluate the correlations between outcome and treatment. A total of 104 patients with physician-diagnosed CRKP were involved in the study. The overall mortality rate was 25.0%. The majority of the infections (84; 80.8%) were hospital acquired. Critical infections received more than one active antibiotic as therapy. Patients treated with fosfomycin combinational therapy were less likely to fail therapy (OR: 4.71, 95% CI: 1.03-21.65, P=0.034) and tended to have a shorter duration of mechanical ventilation. Gender (OR: 4.35, 95% CI: 1.08-3.60, P=0.037), history of chronic obstructive pulmonary disease (OR: 9.35, 95% CI: 0.06-0.19, P=0.007) and peripheral catheter use (OR: 3.00, 95% CI: 0.07-0.19, P=0.002) are risk factors for clinical outcome. Therefore, the use of fosfomycin combinational therapy for treatment of infection due to CRKP appears to be associated with improved survival rate.

Introduction

Infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) have been a serious problem due to limited therapeutic options all around the world (1). Few optimal therapy strategy are available for the infections, making its treatments extremely difficult and leading to poor therapeutic outcomes with the reported mortality rates ranging from 39-72% (2-4). The core issue of managing CRKP infection is to find an effective antibiotic regimen, as carbapenem resistance is often accompanied by resistance to other families of first-line antibiotics, such as beta-lactam inhibitors, quinolones and 3rd/4th generation cephalosporin. Optional antibiotics are usually limited to polymyxins, aminoglycosides, gentamicin, colistin and tigecycline (5,6).

Recently, a study reported that treatment with tigecycline or an aminoglycoside can generate positive outcomes (7). In addition, there are reports indicating that the use of carbapenems in combination with other active agents could contribute to a lower mortality, particularly when the strains have low levels of *in vitro* resistance to those antimicrobials (8). Furthermore, a number of reports suggest that combinational therapies are often more effective than monotherapies (9,10). Therefore, the goal of this retrospective study was to analyze the effect of combinational therapy of fosfomycin and carbapenemase on mortality from sepsis due to CRKP.

Targeted treatment					
Monotherapy	32 (30.8)	11 (42.3)	21 (26.9)	0.141	0.50 (0.20-1.27)
Combination therapy	72 (69.2)	15 (57.7)	57 (73.1)		
Fosfomycin combination	**24 (23.1)**	**2 (7.7)**	**22 (28.2)**	**0.034**	**4.71 (1.03-21.65)**
Other treatment regimens	65 (61.9)	16 (24.6)	49 (75.4)		
Length of ICU stays		15.2±10.5	17.6±12.2	0.355	
Duration of mechanical ventilation		10.7±10.6	10.9±10.9	0.958	

Values in bold are statistically significant. SD, standard deviation; COPD, chronic obstructive pulmonary disorder; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Rapid Emergence of Colistin Resistance and its Impact on Mortality in Healthcare-associated Infections

Mehtap Aydin, Önder Ergönül, Alpay Azap, Hüseyin Bilgin, Güle Aydın, Sema Alp Çavuş, Yusuf Ziya Demiroğlu, Hikmet Eda Çalışkan, Osman Memikoğlu, Şirin Menekşe, Şafak Kaya, Nazlım Aktuğ Demir, İlkay Karaoğlan, Seniha Başaran, Çiğdem Hatipoğlu, Şebnem Erdinç, Emel Yılmaz, Ayhanım Tümtürk, Yasemin Tezer, Hamiyet Demirkaya, Şule Eren Çakar, Şiran Keske, SudaTekin, Cem Yardımcı, Çağla Karakoç, Pınar Ergen, Özlem Azap, Lütfiye Mülazımoğlu, Onur Ural, Füsun Can, Halis Akalın

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We describe the emergence of resistance and predictors of fatality for 1556 cases of healthcare-associated Gram-negative bloodstream infections in 2014 and 2015. The colistin resistance rate in *Klebsiella pneumoniae* was 16.1%, compared with 6% in 2013. 660 (42.4%) cases were fatal. The highest fatality rate was among patients with *Acinetobacter baumannii* bacteremia (58%), followed by *Pseudomonas aeruginosa* (45%), *Klebsiella pneumoniae* (41%), *Enterobacter cloacae* (32%), and *Escherichia coli* (28%). In multivariate analysis, MIC for carbapenem (OR:1.02, CI: 1.01-1.04, p=0.002) and MIC for colistin (OR:1.1, CI:1.03-1.17, p=0.001) were significantly associated with fatality.

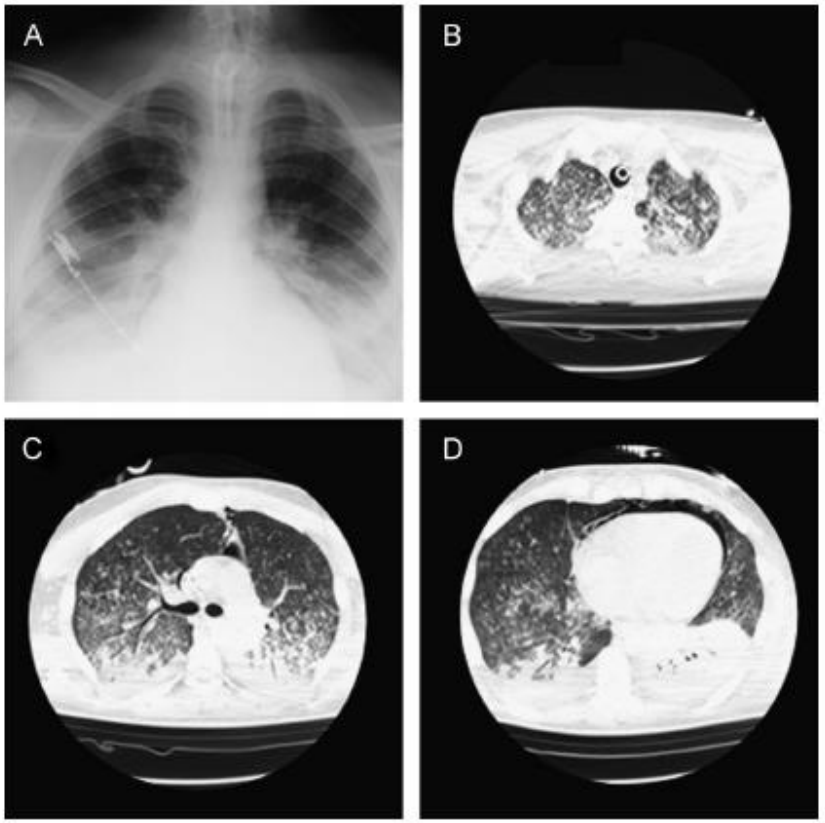
Kolistin Dirençli Kp - VİP

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

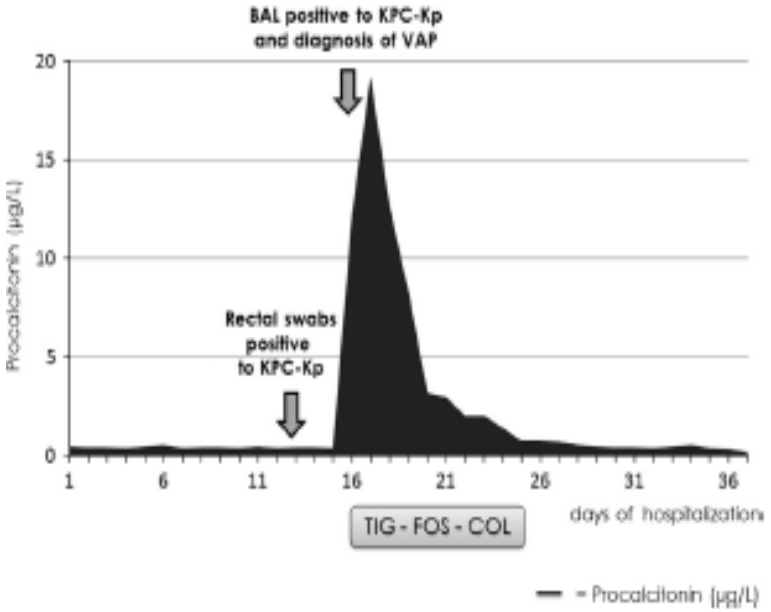


Fig. 2 – Time-course of serum procalcitonin concentration and antibiotic administrations in the intensive care unit. COL: colistin, FOS: fosfomycin, TIG: tigecycline, BAL: bronchoalveolar lavage, KPC-Kp: *Klebsiella pneumoniae* producing KPC-type carbapenemase.

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

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

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

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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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Meta-analysis

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

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

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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

Özet

- Karbapenem dirençli gram negatif bakterilerin ağır infeksiyonlarında kolistin monoterapisi için henüz yeterli kanıt yok
- Kolistin + Meropenem(yüksek doz, uzamış infüzyon ya da sürekli infüzyon)
- Kolistin + Fosfomisin veya AG veya Tigesiklin
- Fosfomisin tek başına kullanılmamalı
- Seftazidim/Avibaktam
- VİP tedavisinde İV tedaviye ek olarak kolistin inhalasyon tedavisi? (Vibrasyon ile nebulizasyon)
- Enzim tipi
- Sinerji testleri
- İlaç düzeylerinin izlenmesi
- PK/PD