KOLİSTİN
Etkinlik - Doz - Toksisite

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

Kolistin

- *Bacillus polymyxa subspecies colistinus*
- Polimiksin A-E, 1947
- Polimiksin B ve Polimiksin E(Kolistin)
- 1950-1980 yılları arasında yoğun kullanım
- Nefrotoksisite
- Kistik fibroz

Kimyasal Yapısı

Kolistin ve Kolistin Metansülfonat

Kolistin Metansülfonatın Sülfametil Grupları

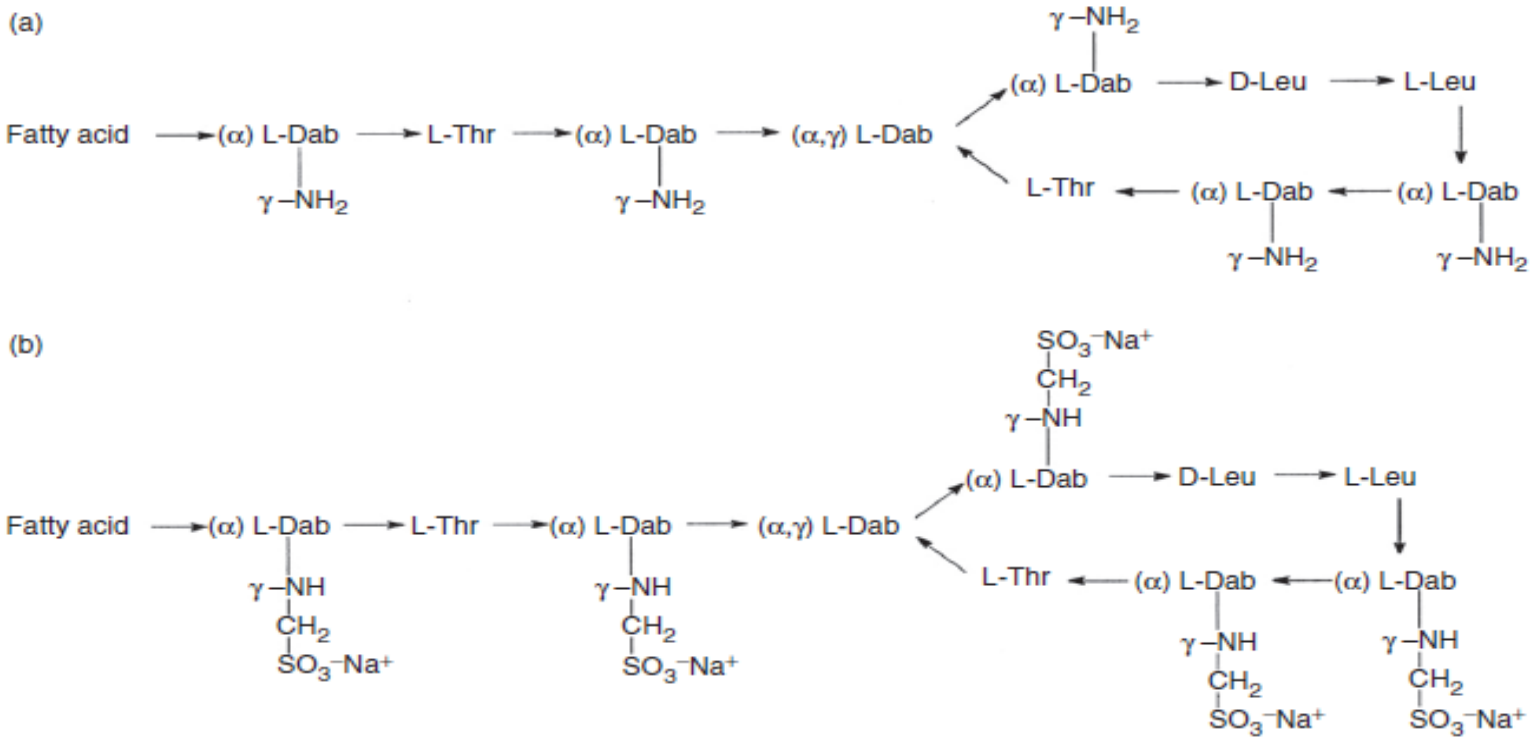


Figure 1. Colistin structures. (A) Structures of colistin A and B. (B) Structures of colistimethate A and B. Fatty acid: 6-methyloctanoic acid for colistin A and 6-methylheptanoic acid for colistin B; Thr = threonine; Leu = leucine; Dab = α,γ-diaminobutyric acid; α and γ indicate the respective amino groups involved in the peptide linkage. (Modified from Li *et al.*[4]).

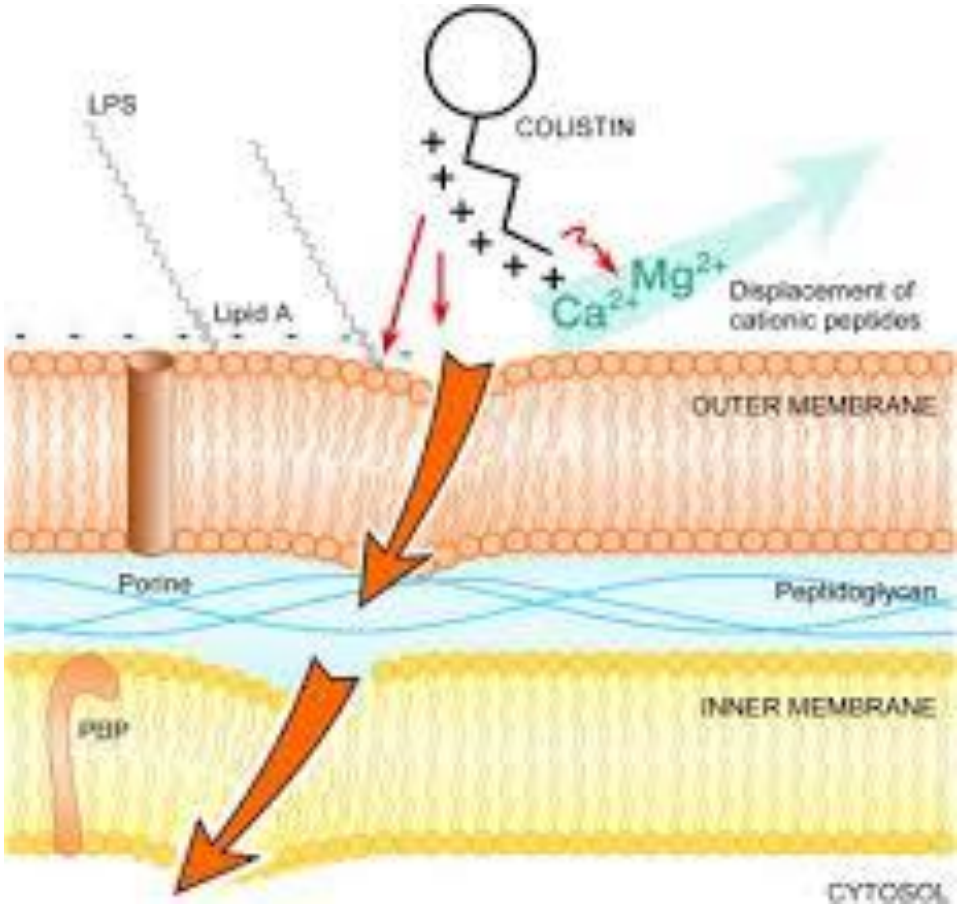
Etki Mekanizması

- Bakterisidal etkisi son derece hızlı
- Konsantrasyona bağımlı etki
- Anti-endotoksin etki

Etki Mekanizması

- Hedefi dış hücre membranıdır
- Dış membranın koruyucu etkisi = LPS
- LPS: Hidrofobik ve/veya büyük antibiyotiklerin geçişini engeller

- Polimiksin gram negatif bakteriler üzerine 2 basamaklı mekanizma ile tamamen deterjana benzer bir etki gösterir
- Katyonik peptid olan kolistin, bakteri dış membranındaki anyonik LPS ile elektrostatik olarak etkileşir
- LPS'nin fosfat grupları içindeki Ca ve Mg iyonlarını dışarı çıkarır
- Permeabilite bozukluğu sonucu ölüm


LPS
COLISTIN
Lipid A
Mg^{2+}
Ca^{2+}
Displacement of cationic peptides
OUTER MEMBRANE
Porine
Peptidoglycan
INNER MEMBRANE
PBP
CYTOSOL

KOLİSTİN – KOLİSTİMETAT SODYUM

1 mg Kolistin baz = yaklaşık 2,4 mg Kolistimetat sodyum

COLİMYCIN / KOÇAK'ta: 384 mg Kolistimetat sodyum var

1 mg Kolistin baz = 30.000 IU

1 mg Kolistimetat sodyum = 12.500 IU

1.000.000 IU = 80 mg Kolistimetat sodyum

1.000.000 IU = 33.3 mg Kolistin Baz

150 mg Kolistin = 4.500.000 IU

Kolistin (Sanford, 2016)

- FK/FD: f AUC/MIC
- Tek doz sonrası(150 mg baz IV) Cmax 5-7.5 µg/ml (Sanford, 2015)
- Proteine bağlanma %50
- Serum yarılanma ömrü 6.3-12 saat
- Vd 0.17 L/kg
- Gebelikte C grubu
- Aminoglikozidler, AmB-d, Vankomisin ile birlikte nefrotoksisite artışı

Kolistin

- Kararlı düzeylere 2.günde ulaşıyor
- Yükleme dozu gerekli
- CMS renal yoldan atılıyor
- Kolistin tübüler reabsorbsiyona uğruyor
- CMS ve kolistin hemodiyalizle atılıyor
- Sürekli hemofiltrasyonda 6 MU/gün

Couet W et al. Clin Pharmacol Ther 2011
Plachouras D et al. Antimicrob Agents Chemother 2009
Garonzik SM et al. Antimicrob Agents Chemother 2011

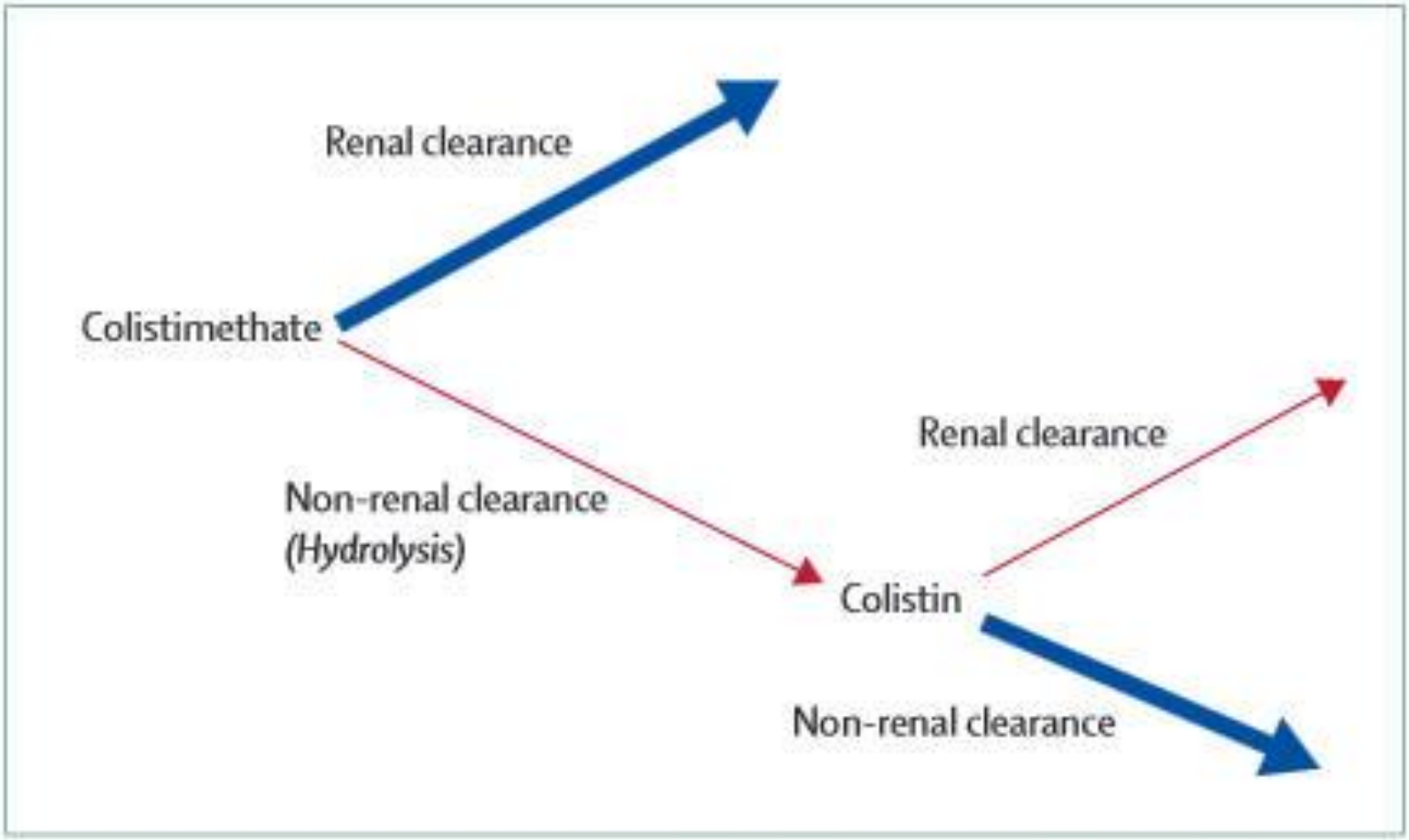


Figure 2: **Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium**

Kolistin - Doz Ne Olmalı ?

- Yükleme dozu (Kolistin baz)

  2.5 x 2 x Vücut ağırlığı (ideal veya gerçek-düşük olanı kullanılır)

- İdame doz (yükleme dozundan 12 saat sonra geçilmesi ve 8-12 saatte bir verilmesi önerilmektedir)

  2.5 x [(1.5 x CrCl) + 30]

- CrCl= CrCl X vücut yüzeyi /1.73 m^2
- İdame günlük maksimum doz ≤ 340 mg

Sanford, 2016

Colimycine - Prospektüs

- Yükleme dozu

  -5 mg/kg (300 mg'ı geçmeyecek şekilde)
  -Kreatinin klirensinden bağımsız bir şekilde
  -Diyalize girmeyen tüm hastalar için

Spektrum

- *Acinetobacter* spp.
- *Pseudomonas aeruginosa*
- *Klebsiella* spp.
- *Enterobacter* spp.
- *Escherichia coli*
- *Stenotrophomonas maltophilia*

Kolistine İntrensek Dirençli Bakteriler

- *Serratia* spp.
- *Proteus* spp.
- *Providencia* spp.
- *Burkholderia cepacia*
- *Morganella* spp.
- *Moraxella catarrhalis*

Kolistin – Heterorezistans

- *A.baumannii*'de kolistine karşı heterorezistans

Li J et al. Antimicrob Agents Chemother 2006

- Kolistin – Heterorezistans
  -K. pneumoniae
  -A. baumannii
  -P. aeruginosa

Bialvaei AZ et al. Curr Med Res Opin 2015

Enterobacteriaceae

Miscellaneous agents	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbered notes rela Lettered notes relate
	S ≤	R >		S ≥	R <	
Chloramphenicol	8	8	30	17	17	1. Fosfomycin MICs must
Colistin	2	2		Note^	Note^	dilution methods). Follow
Daptomycin	-	-		-	-	2. Trimethoprim:sulfamet
Fosfomycin iv	32[1]	32[1]		IP	IP	~~2/B. Breakpoints apply to~~
Fosfomycin oral (uncomplicated UTI only)	32[1]	32[1]		IP	IP	
Fusidic acid	-	-		-	-	A. Use an MIC method.
Metronidazole	-	-		-	-	
Mupirocin	-	-		-	-	
Nitrofurantoin (uncomplicated UTI only), *E. coli*	64	64	100	11	11	
Rifampicin	-	-		-	-	
Spectinomycin	-	-		-	-	
Trimethoprim (uncomplicated UTI only)	2	4	5	18	15	
Trimethoprim-sulfamethoxazole[2]	2	4	1.25-23.75	16	13	

Pseudomonas spp.

EUCAST Clinical Breakpoint

Miscellaneous agents	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	Numbered notes relate to general comments and/or MIC bre Lettered notes relate to the disk diffusion method.
Chloramphenicol	-	-		-	-	1. Infections caused by wild type isolates (ECOFF 128 mg/L) have been tre
Colistin	4	4		Note[A]	Note[A]	A. Use an MIC method.
Daptomycin	-	-		-	-	
Fosfomycin iv[1]	-	-		-	-	
Fosfomycin oral[1]	-	-		-	-	
Fusidic acid	-	-		-	-	
Metronidazole	-	-		-	-	
Mupirocin	-	-		-	-	
Nitrofurantoin (uncomplicated UTI only)	-	-		-	-	
Rifampicin	-	-		-	-	
Spectinomycin	-	-		-	-	
Trimethoprim (uncomplicated UTI only)	-	-		-	-	
Trimethoprim-sulfamethoxazole	-	-		-	-	

Acinetobacter spp.

Miscellaneous agents	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	Numbered notes rela Lettered notes relate
Chloramphenicol	-	-		-	-	1. Trimethoprim:sulfamet
Colistin	2	2		Note[A]	Note[A]	A. Use an MIC method.
Daptomycin	-	-		-	-	
Fosfomycin iv	-	-		-	-	
Fosfomycin oral	-	-		-	-	
Fusidic acid	-	-		-	-	
Metronidazole	-	-		-	-	
Mupirocin	-	-		-	-	
Nitrofurantoin (uncomplicated UTI only)	-	-		-	-	
Rifampicin	-	-		-	-	
Spectinomycin	-	-		-	-	
Trimethoprim (uncomplicated UTI only)	-	-		-	-	
Trimethoprim-sulfamethoxazole[1]	2	4	1.25-23.75	16	13	

Kombinasyon-İn vitro Sonuçlar

- *A.baumannii*
  - Kolistin + rifampisin
  - Kolistin + amikasin
  - Kolistin + imipenem
  - Kolistin + doksisiklin

Giamarellos-Bourboulis E et al. Diagn Microbiol Infect Dis 2001
Timurkaynak F et al. Int J Antimicrob Agents 2006
Haddad FA et al. Eur J Clin Microbiol Infect Dis 2005
Bratu S et al. Eur J Clin Microbiol Infect Dis 2005

Acinetobacter baumannii - Polimiksin İn vitro Sinerji

- 39 yayın ve 15 bildiri
- Zaman - ölüm eğirisi
- Kolistin + Karbapenem %77 sinerjik
- Meropenem > İmipenem

Zusman O et al. Antimicrob Agents Chemother 2013

Acinetobacter baumannii – Polimiksin İn vitro Sinerji(%)

- 70 yayın ve 31 bildiri
- 1484 *A. baumannii* suşu

	Zaman-Ölüm	Dama Tahtası	E-test
POL+CAR	80.6	39.6	32.4
POL+RİF	57.2	60.3	30.8
POL+TİG	41.6	10.4	13.5
COL+GLP	70.8	56	-
POL+SUL	70.8	54.1	-

Wentao N et al. Int J Antimicrob Agents 2015

Kolistin Tedavisi

- 2000-2007, Atina
- MDR gram negatif, 258(222'si YBÜ)
  - -170 *A. baumannii*
  - -68 *P. aeruginosa*
  - -18 *K. pneumoniae*
  - -1 *S. maltophilia*
  - -1 *E. cloacae*
- 135 izolat sadece kolistine duyarlı
- 155 pnömoni, 33 bakteriyemi, 22 abdominal enfeksiyon

Falagas ME et al. Int J Antimicrob Agents 2010

Kolistin Tedavisi

- Ortalama kolistin süresi 17.9 gün
- Tedavi başarısı
  - -Kolistin, Kolistin + Meropenem %83.3
  - -Kolistin + Pip/Tazo %64.7
  - -Kolistin + Amp/Sulb %75
  - -Kolistin + Diğer %61.3
  - -Kolistin = Kolistin + Meropenem

- Yüksek doz – Düşük mortalite

Falagas ME et al. Int J Antimicrob Agents 2010

Yükleme ve Yüksek Doz: Klinik Sonuç

- 300 mg yükleme – 2x150 mg idame
- 28 atak, 18 KDE ve 10 VİP
- *A.baumannii(*13), *K.pneumoniae*(13), *P.aeruginosa*(2)
- 14 monoterapi, 14 kombinasyon(AG veya Karbapenem)
- Klinik kür: %82.1
- Akut böbrek hasarı %17.8

Dalfino L et al. Clin Infect Dis 2012

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

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Review

Intravenous colistin combination antimicrobial treatment vs. monotherapy: 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 Centre, Athens, Greece
[c] Hellenic Police Health Headquarters, Athens, Greece
[d] Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

Kolistin Monoterapi - Kombinasyon

- 32 çalışmanın meta-analizi
- 29 gözlemsel ve 3 randomize
- 2328 hasta
- *Acinetobacter baumannii* ve *Klebsiella pneumoniae*
- Kombinasyon ile mortalite azalmıyor
- Yüksek doz(>6 MU) kolistin ile kombinasyonda daha az mortalite
- Asya'daki çalışmalarda kombinasyon ile daha az mortalite

Vardakas KZ et al. Int J Antimicrob Agents 2018

Kolistin
Monoterapi - Kombinasyon

- Bakteriyemilerde kombinasyonda mortalite daha az
- *Acinetobacter* spp. infeksiyonlarında mortalite daha az

Vardakas KZ et al. Int J Antimicrob Agents 2018

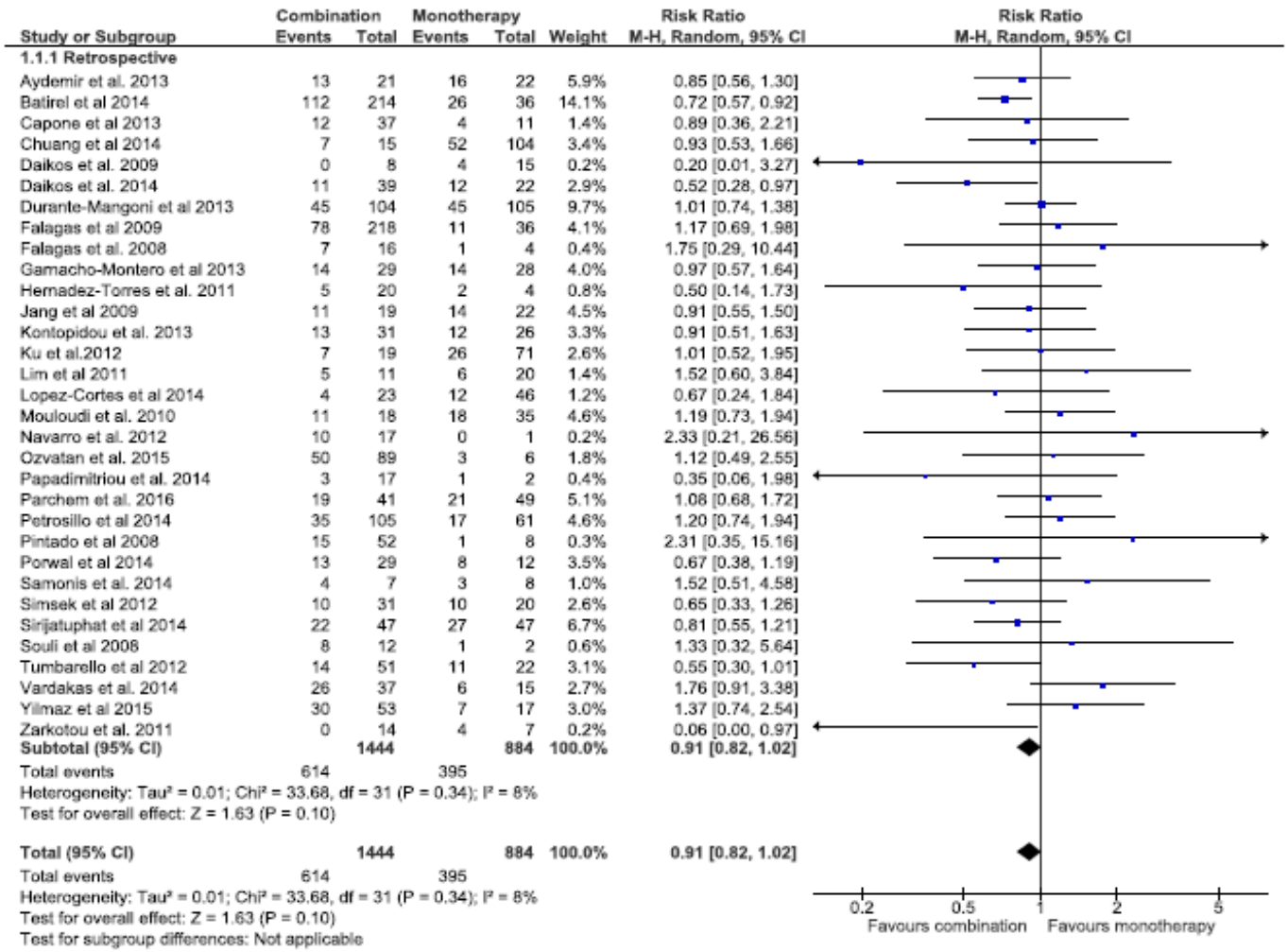

Fig. 2. Forest plot depicting the risk ratios of mortality among patients treated with intravenous colistin in combination with other antibiotics vs intravenous colistin monotherapy. Vertical line, 'no difference' point between the two regimens; squares, risk ratios; diamonds, pooled risk ratios for all studies; horizontal lines, 95% confidence intervals (CI). The area of each square is proportional to the weight given to the study. Risk ratios are indicated by the centre of each square. M-H, Mantel-Haenszel.

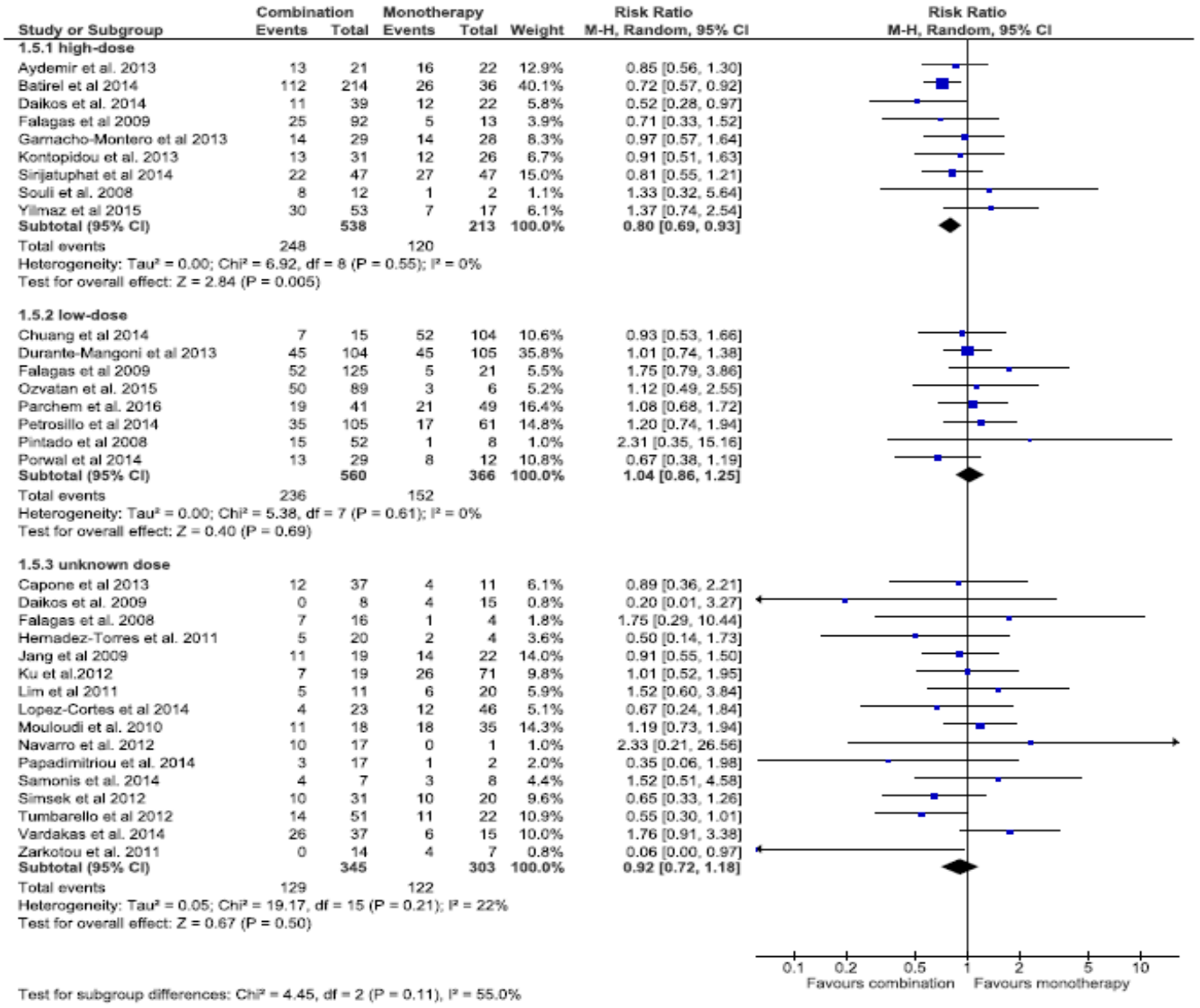

Fig. 3. Forest plot depicting the risk ratios of mortality among patients treated with intravenous colistin in combination with other antibiotics vs. intravenous colistin monotherapy according to colistin dose. Vertical line, 'no difference' point between the two regimens; squares, risk ratios; diamonds, pooled risk ratios for all studies; horizontal lines, 95% confidence intervals (CI). The area of each square is proportional to the weight given to the study. Risk ratios are indicated by the centre of each square. M-H, Mantel-Haenszel.

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

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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**

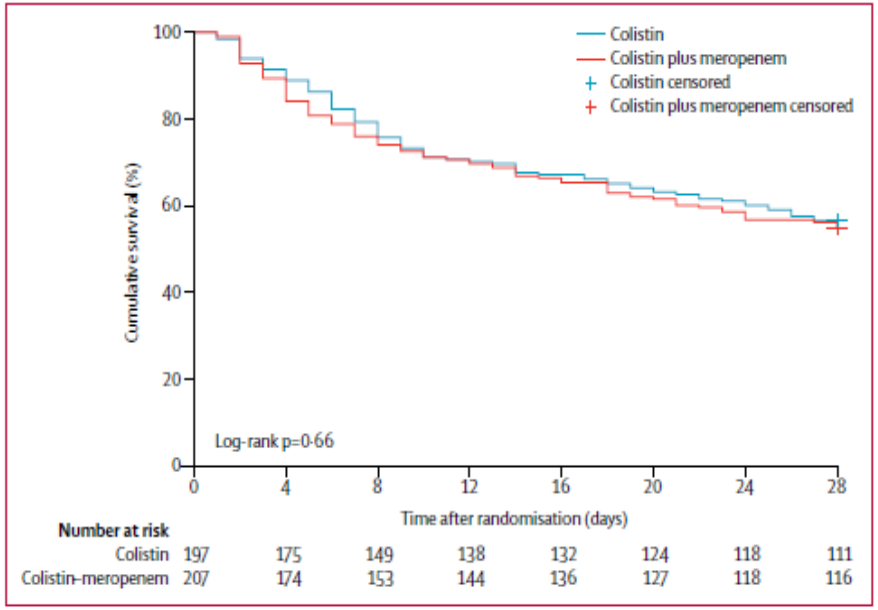

Figure 2: **Survival analysis to day 28 after randomisation**

	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

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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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) ■■–■■

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Review

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

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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	Inhaled/Intravenous Total	Intravenous Events	Intravenous 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						

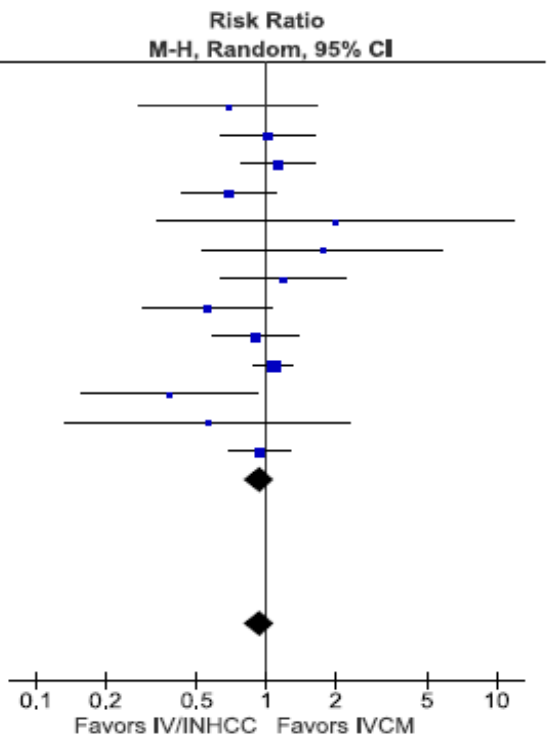

Fig. 2. Forest plot depicting the risk ratios (RR) of mortality among patients treated with IV/INHCC and IVCM. *(Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI. The areas of squares are proportional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

Menenjit ve Kolistin İntraventriküler veya İntratekal Uygulama

Acinetobacter Menenjiti

- İntravenöz uygulama sonrası BOS konsantrasyonları çok iyi çalışılmamış
- Sadece intravenöz yol ile tedavi edilen olgular var(3 x 3 MIU veya 4 x 1.25 mg/kg)
- İntravenöz tedavi ile başarısız olgular da var (2 x 2.5 MIU veya 4 x 2 MIU)

Kim Baek-Namet al. Lancet Infect Dis 2009

MSS Enfeksiyonları

- 31 çalışma, 60 hasta, 64 atak
- Sadece polimiksin tedavisi
  - İntraventriküler/intratekal 11 atak
  - Kombinasyon(+IV) 25 atak
- İntraventriküler/intratekal doz
  - Polimiksin B ve kolistin
  - 20000-250000 IU
  - 5000-120000 IU(bebek-çocuk)
- Süre 1-9 hafta

Falagas ME et al. Int J Antimicrob Agents 2007

MSS Enfeksiyonları

- İyileşme 51/64(%80)
  - Erişkin 27/34(%79)
  - Çocuk 24/30(%80)

  P.aeruginosa 27/31(%87)
  A.baumannii 10/11(%91)
  K.pneumoniae 5/8(%63)
- Toksisite 17/60
  - En yaygın meninks irritasyonu: 12 hasta

Acinetobacter Menenjiti

- 1990-2009,18 makale
- 30 hastada 32 atak (27 erişkin hasta)
- Son tedavi rejimi olarak kolistin
  - -Sadece topikal olarak 8 hastada
  - -Sistemik + topikal 13 hastada
- Erişkinde 1.6 mg-20 mg/gün, 3-42 gün
- Çocuklarda 1-4 mg/gün
- Topikal tedavi alan tüm hastalarda BOS'ta bakteri eradike edilmiş

Cascio A et al. Int J Infect Dis 2010

Acinetobacter Menenjiti

- Eradikasyon için ortanca süre 4.1 gün(1-15)
- %75 olguda 5.günden önce eradikasyon
- 5 hastada topikal uygulama ile ilişkili yan etki-3 hastada kültür negatif pleositoz
  - -1 hastada nonspesifik nörolojik belirtiler
  - -1 hastada konvülsiyon(IT 8 mg)
- İntraventriküler yolda intratekal yola göre daha az yan etki
- Gecikmeden topikal uygulama

Cascio A et al. Int J Infect Dis 2010

IDSA Önerileri

- 10 mg/gün (intraventriküler)
- V-P şant öncesi 10-14 gün negatif kültür

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

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

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

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

J Antimicrob Chemother 2017; **72**: 1985–1990
doi:10.1093/jac/dkx070 Advance Access publication 21 April 2017

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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Diagnostic Microbiology and Infectious Disease

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

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

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

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.

Nefrotoksisite

- Eski çalışmalar(1962-1977)
  - Genellikle IM verilmiş
  - Yüksek dozlar
  - %10.5-50(%20.2-%36)
- Yeni çalışmalar
  - Nefrotoksisite tanımında farklılıklar
  - Kolistin %14-18.6
  - Polimiksin B %10-14
- Doza bağımlı, membran permeabilite artışı, akut tübüler nekroz

Falagas ME et al. Critical Care 2006

Nefrotoksisite

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

Javan AO et al. Eur J Clin Pharmacol 2015
Spapen H et al. Ann Intensive Care 2011

Nefrotoksisite

- %48 oranında
- RIFLE skoru

Temoçin F et al. Jpn J Infect Dis 2015

- %40 oranında
- RIFLE skoru

Tigen ET et al. Indian J Crit Care Med 2016

- %70 oranında
- RIFLE skoru

Özkarakaş H et al. Turk J Med Sci 2017

Acinetobacter baumannii, VİP(67) ve KDE(27)

	Toplam (n=94)	Yaşayanlar (n=65)	Ölenler (n=29)	P değeri
Yaş (yıl)	51,5±17.70	51,2±19,44	51,2±17,0	>0.05
Cinsiyet (K/E)	33/61	22/43	11/18	>0.05
APACHE II skoru	20.17±7.99	20,82±8.08	18.67±7.71	>0.05
GCS	7.71±4.54	7.52±4.59	8.13±4.48	>0.05
APACHE II≥20 (n,%)	49 (53,26)	38 (77,6)	11 (22,4)	
SOFA_tedavi başlangıç günü	8.27±3.57	7,80±3,44	9,34±3,69	0.023*
SOFA_tedavi sonu/ 10. gün	8.51±4.21	7.27±3.82	11.15±3.83	0.001*

Kolistin dozu (MÜ) (ort/gün)	3.66±1.83	3,81±1,89	3,31±1,69	>0.05
Kolistin süresi (gün)	12 (1-49)	7,71±3,98	15,50±8,13	0.001*
Renal toksisite (n)	12	5	7	0.05*
Doz modifikasyonu gereksinimi (n)	11	4	7	0.05*
Enfeksiyonun gidişi (n) Kür tedavi İyileşme Rekürrens İndetermine Başarısız	 39 11 1 11 32	 37 11 1 4 12	 2 0 0 7 20	
Bakteriyel eradikasyon (n)	40	38	2	0.001*
Bakteriyel persistens (n)	43	24	19	0.001*
28. gün mortalitesi (n)	29 (%30,9)			

Nefrotoksisite - Risk Faktörleri

- Doz
- Kullanım süresi
- Diğer nefrotoksik ajanlar
- Hastalığın ağırlığı-Yüksek APACHE II skoru
- Yaş
- Cinsiyet
- Altta yatan hastalık
- Hipoalbuminemi
- Hiperbilirubinemi

Javan AO et al. Eur J Clin Pharmacol 2015

Nörotoksisite

- Eski çalışmalar
  - Parestezi %7.3-27
  - Apne
  - Nöromuskuler blok
- Yeni çalışmalar
  - Nörotoksisite yok

Falagas ME et al. Critical Care 2006

Nörotoksisite

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

- Doza bağımlı ve geriye dönebilen

Gregoire G et al. Clin Pharmacokinetic 2017

Diğer Yan Etkiler-İlaç Etkileşimleri

- Alerjik reaksiyonlar %2
- İnhalasyon
  - Boğaz ağrısı
  - Öksürük
  - Bronkospazm
  - Göğüste sıkışma
- İlaç Etkileşimleri
  - Nöromuskuler blok yapan ilaçlar
  - Aminoglikozid

Falagas ME et al. Critical Care 2006