POLİMİKSİNLER

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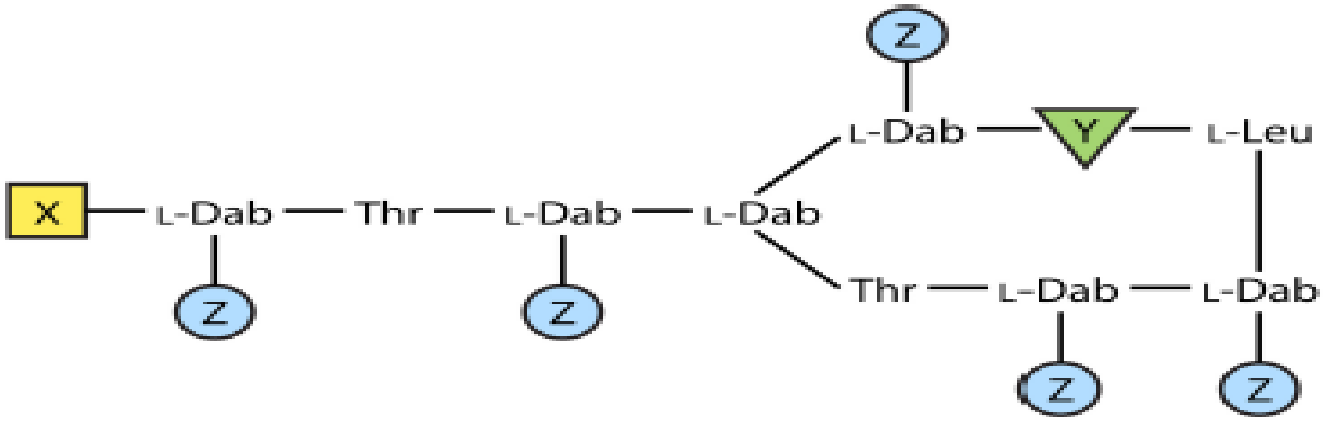
Polymyxins: Antibacterial Activity, Susceptibility Testing, and Resistance Mechanisms Encoded by Plasmids or Chromosomes

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



Dab, Diaminobutyric acid; Thr, Threonine; Phe, Phenylalanine; Leu, Leucine; L, Levogyre; D, Dextrogyre

X — Fatty acid residue differing between the components of the mixtures: 6-methyloctanoic acid for colistin A and polymyxin B1, and 6-methylheptanoic acid for colistin B, and polymyxin B2

Y — Aminoacid differing between colistin and polymyxin B: D-Leu for colistin, and D-Phe for polymyxin B

Z — Groups differing between colistin/polymyxin B and colistimethate: $-NH_2$ for colistin and polymyxin B, and $-NH-CH_2-SO_3H$ for colistimethate

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

Polimiksin-B

- Kimyasal yapı, etki mekanizması ve spektrumu benzer
- Pol-B sülfat formunda ve doğrudan etkili
- Kolistin ise kolistimetat şeklinde prodrug
- Klinik etkinlik açısından anlamlı farklılık yok
- Günlük doz: 2 x 1.25 mg/kg

Pogue JM et al. Clin Microbiol Infect 2017

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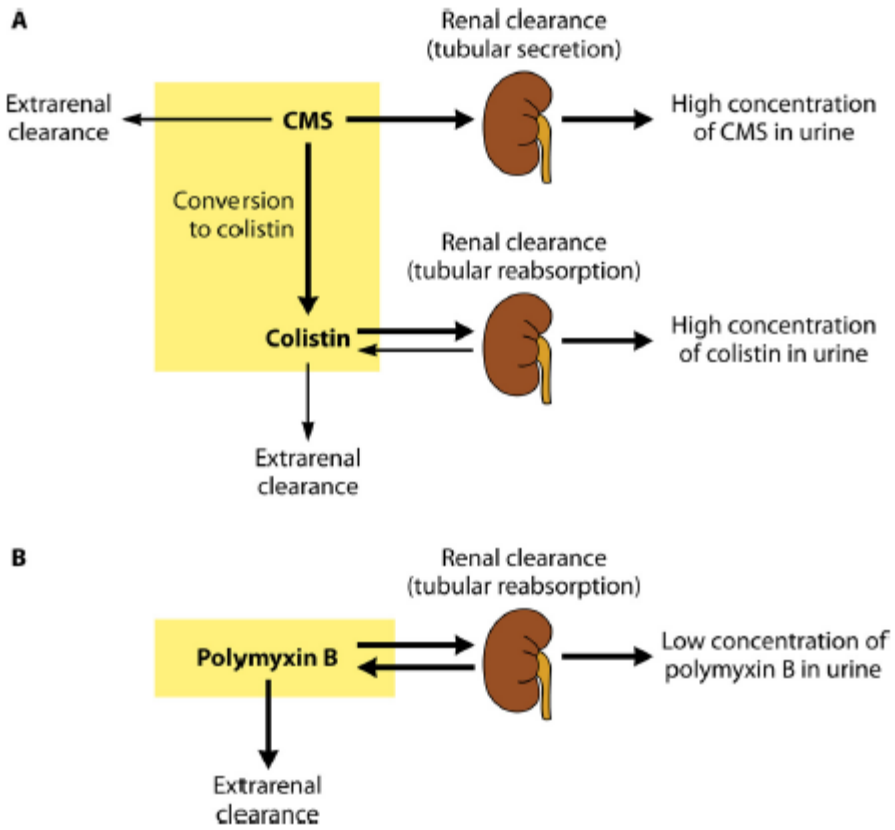


FIG 2 Overview of the pharmacokinetic pathways for colistimethate (CMS) and colistin (A) and for polymyxin B (B). The thicknesses of the arrows indicate the relative magnitudes of the respective clearance pathways when kidney function is normal. CMS includes fully and all partially methanesulfonated derivatives of colistin. After administration of CMS, extensive renal excretion of the prodrug occurs, with some of the excreted CMS being converted to colistin within the urinary tract. (The figure is based in part on data from reference 7.)

Kolistin

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

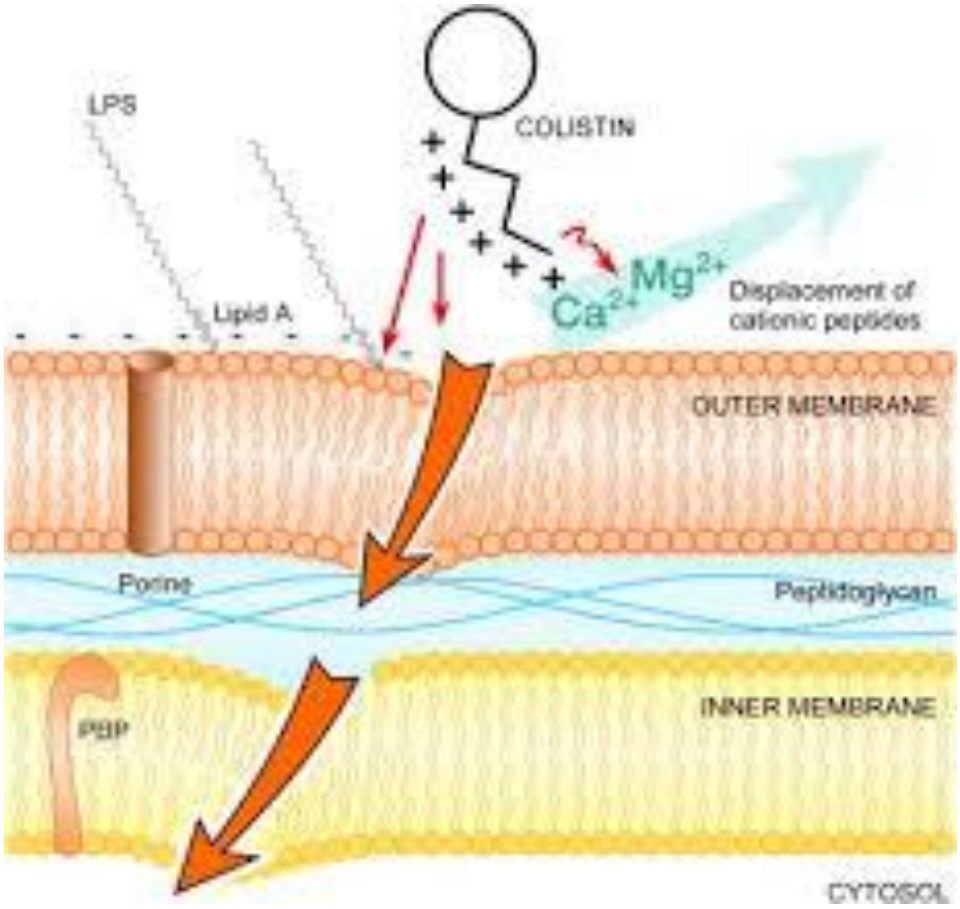
Etki Mekanizması

- 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

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

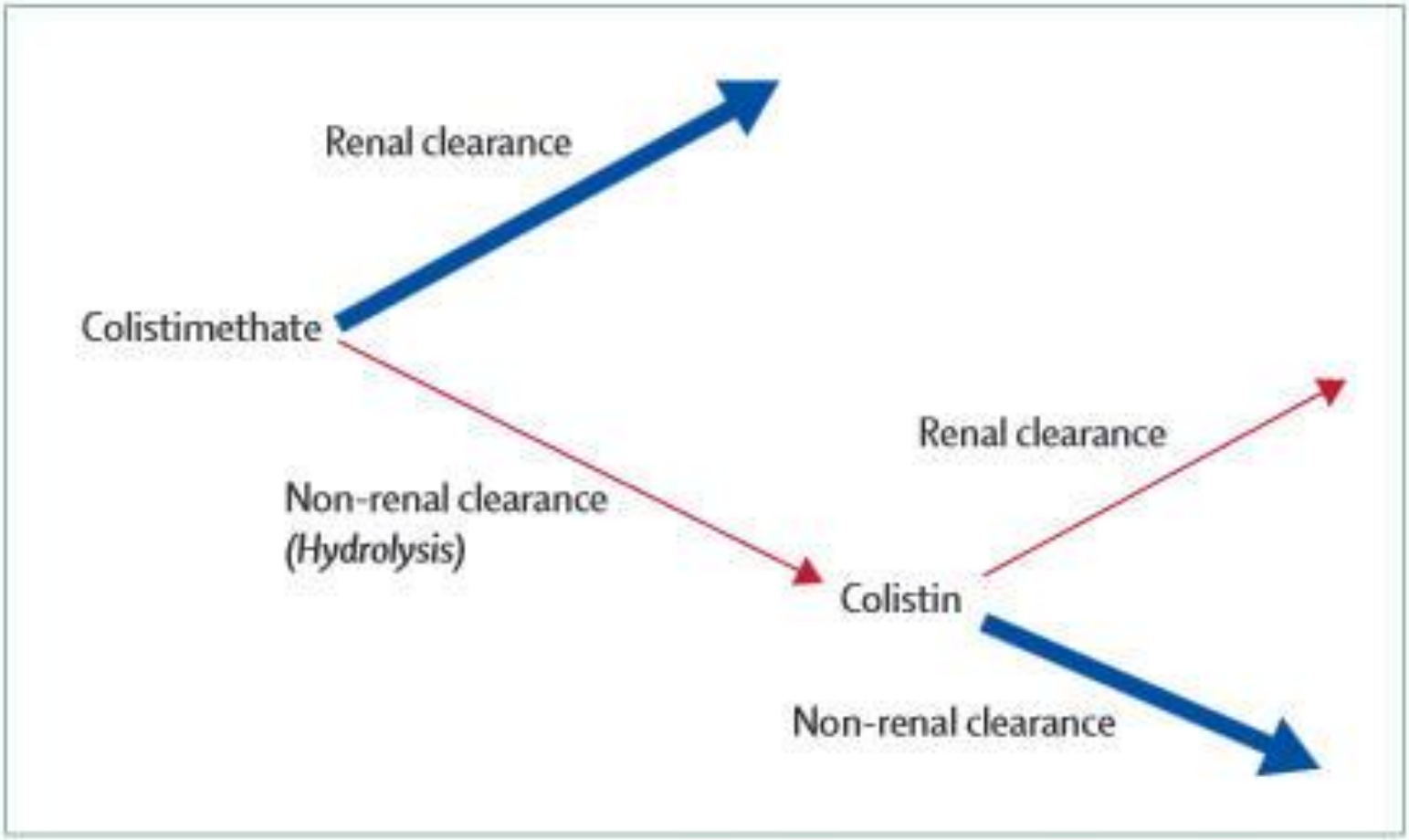


Figure 2: **Schematic representation of the disposition of colistimethate and the colistin generated from it in the body, following administration of colistimethate sodium**

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

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*

Acinetobacter baumannii - Polimiksin İn vitro Sinerji

- 39 yayın ve 15 bildiri
- Zaman - ölüm eğrisi
- 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

J Antimicrob Chemother 2017; **72**: 29–39
doi:10.1093/jac/dkw377 Advance Access publication 13 September 2016

Journal of Antimicrobial Chemotherapy

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

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Objectives: The objective of this study was to summarize available data on polymyxin-based combination therapy or monotherapy for carbapenem-resistant Gram-negative bacteria.

Methods: This is a systematic review. We included observational studies and randomized controlled trials (RCTs) comparing polymyxin monotherapy versus polymyxin-based combination therapy in adult patients with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria. Only named antibiotic regimens were included. The primary outcome was 30 day mortality. Unadjusted OR (uOR) and adjusted OR where available with 95% CI were pooled in random-effects meta-analyses.

Results: Twenty-two studies including 28 comparisons were included. Polymyxin monotherapy was associated with a uOR of 1.58 (95% CI=1.03–2.42) for mortality compared with polymyxin/carbapenem combination therapy (seven observational studies, 537 patients), without heterogeneity. Subgrouping studies to serious and critical risk of bias resulted in uORs of 0.94 (95% CI=0.42–2.09) and 1.94 (95% CI=1.17–3.23), respectively. Mortality was significantly higher with polymyxin monotherapy compared with combination therapy with tigecycline, aminoglycosides or fosfomycin (potentially double-coverage regimens): uOR of 1.57 (95% CI=1.06–2.32) overall (10 observational studies and 1 RCT, 585 patients, no heterogeneity) and uOR of 2.09 (95% CI=1.21–3.6) for *Klebsiella pneumoniae* bacteraemia (7 observational studies, 285 patients, no heterogeneity); very low quality evidence. Two RCTs and one observational study assessing rifampicin/colistin combination therapy for *Acinetobacter baumannii* infections showed no difference in mortality compared with colistin monotherapy; moderate quality evidence.

Conclusions: The significant association observed in observational studies between polymyxin monotherapy and mortality cannot be taken as proof of combination therapy effects due to the low quality of the evidence. The only three RCTs to date show no effect of rifampicin/colistin or fosfomycin/colistin on mortality for *Acinetobacter* infections.

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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

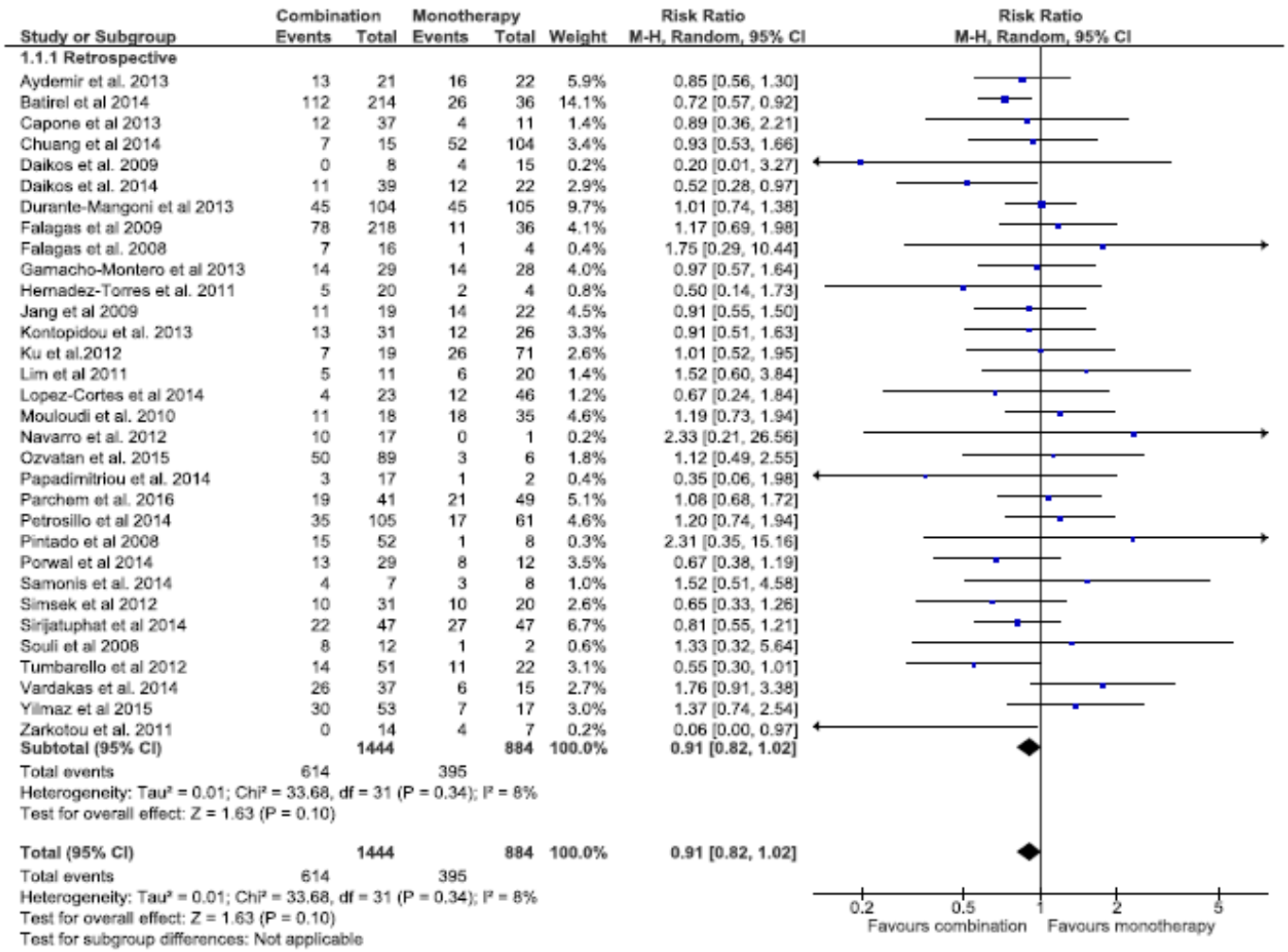

Fig. 2. Forest plot depicting the risk ratios of mortality among patients treated with intravenous colistin in combination with other antibiotics vs intravenous colistin monotherapy. Vertical line, 'no difference' point between the two regimens; squares, risk ratios; diamonds, pooled risk ratios for 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.

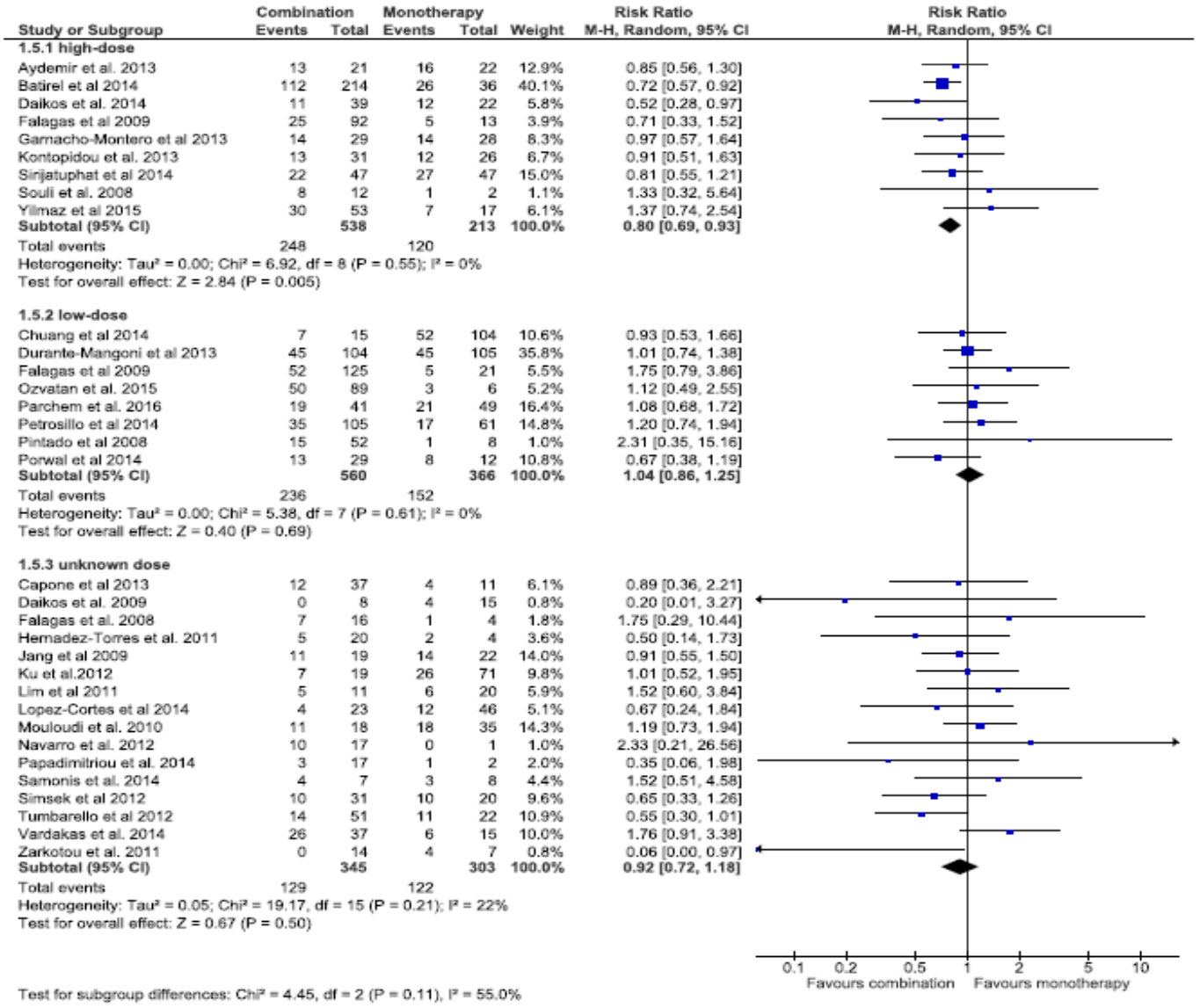

Fig. 3. Forest plot depicting the risk ratios of mortality among patients treated with intravenous colistin in combination with other antibiotics vs. intravenous colistin monotherapy according to colistin dose. Vertical line, 'no difference' point between the two regimens; squares, risk ratios; diamonds, 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

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

Kolistin
Monoterapi - Kombinasyon

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

Paul M et al. Lancet Infect Dis 2018

Kolistin
Monoterapi - Kombinasyon

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

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

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

Table 1: **Patient and infection characteristics**

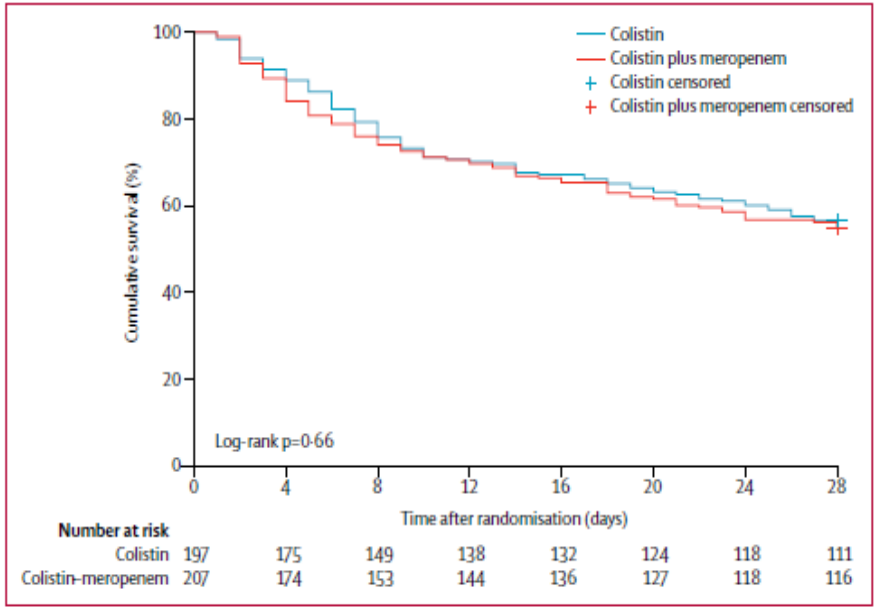

Figure 2: **Survival analysis to day 28 after randomisation**

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

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

Table 3: Adverse events

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

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

Table 4: **Subgroup analyses**

Kolistin
Monoterapi - Kombinasyon

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

VİP: Kolistin – İnhalasyon?

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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

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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Journal of Infection

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

Review

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

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

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[d] *Department of Medicine, Tufts University School of Medicine, Boston, MA, USA*

Kolistin: IV + İnhalasyon

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

Vardakas KZ et al. J Infect 2018

Study or Subgroup	Inhaled/Intravenous Events	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						

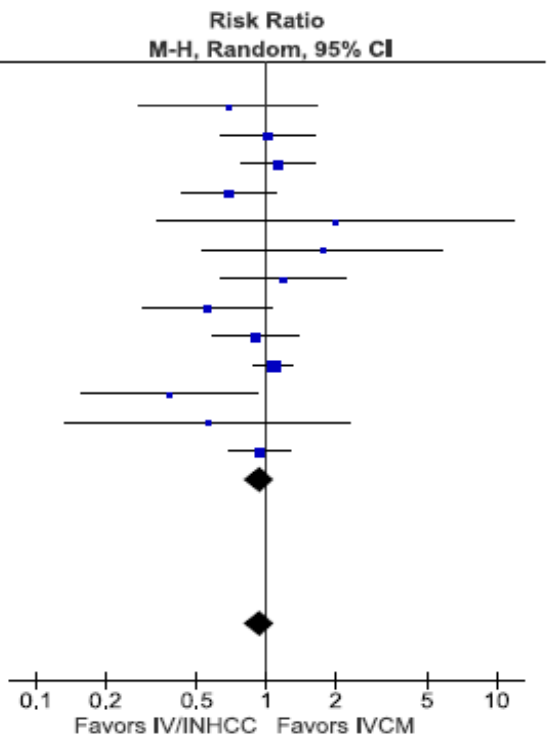

Fig. 2. Forest plot depicting the risk ratios (RR) of mortality among patients treated with IV/INHCC and IVCM. *(Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI. The areas of squares are proportional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

- 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

- 2010-2013, 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

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

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
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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

Diagnostic Microbiology and Infectious Disease 76 (2013) 335–338

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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

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

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

Avrupa'da Kolistin Direnci

- İtalya: KPC(+) *K. pneumoniae* suşlarında kolistin direnci %23
- İspanya: Metallo-Beta Laktamaz (+) *K.pneumoniae* suşlarında kolistin direnci %25

Giske CG. Clin Microbiol Infect 2015

Journal of Hospital Infection 98 (2018) 260–263

Available online at www.sciencedirect.com

Journal of Hospital Infection

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

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

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Table I

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

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

Acta Microbiologica et Immunologica Hungarica
DOI: 10.1556/030.65.2018.042

HIGH RATE OF COLISTIN AND FOSFOMYCIN RESISTANCE AMONG CARBAPENEMASE-PRODUCING *ENTEROBACTERIACEAE* IN TURKEY

SERAP SÜZÜK YILDIZ[1]*, BANU KAŞKATEPE[2], HÜSNİYE ŞİMŞEK[1] and FATMA MUTLU SARIGÜZEL[3]

Table I. Distribution of isolates according to their resistance properties

Bacteria	Number (%)	ESBL	AmpC	OXA-48	NDM-1	KPC	OXA-48 and NDM-1	OXA-48 and KPC
K. pneumoniae	134 (91.16)	26 (86.67)	5 (62.5)	115 (92.00)	3	1	13 (81.25)	1
E. coli	11 (7.48)	3 (10.00)	2 (25.00)	8 (6.4)			3 (18.75)	
E. cloacae	1 (0.68)	1 (3.33)	1 (12.5)	1 (0.8)				
S. marcescens	1 (0.68)			1 (0.8)				
Total	147	30 (20.41)	8 (5.44)	115 (78.23)	3 (2.04)	1 (0,68)	16 (10.88)	1 (0.68)

Note: ESBL: extended spectrum beta-lactamase; AmpC: ampC beta-lactamases; NDM: New Delhi metallo-beta-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase.

Kolistin direnci %76.19

Fosfomisin direnci %67.35

Kolistin Direnci

- *A. baumannii*
  -PmrAB
  -LPS yapımında azalma
- *P. aeruginosa*
  -PmrAB
  -PhoPQ
- *K. pneumoniae* (KPC+)
  -mgrB

Bialvaei AZ et al. Curr Med Res Opin 2015

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

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

Summary

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

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

Findings Polymyxin resistance was shown to be singularly due to the plasmid-mediated *mcr-1* gene. The plasmid carrying *mcr-1* was mobilised to an *E coli* recipient at a frequency of 10^{-1} to 10^{-3} cells per recipient cell by conjugation, and maintained in *K pneumoniae* and *Pseudomonas aeruginosa*. In an in-vivo model, production of MCR-1 negated the efficacy of colistin. MCR-1 is a member of the phosphoethanolamine transferase enzyme family, with expression in *E coli* resulting in the addition of phosphoethanolamine to lipid A. We observed *mcr-1* carriage in *E coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection.

Interpretation The emergence of MCR-1 heralds the breach of the last group of antibiotics, polymyxins, by plasmid-mediated resistance. Although currently confined to China, MCR-1 is likely to emulate other global resistance mechanisms such as NDM-1. Our findings emphasise the urgent need for coordinated global action in the fight against pan-drug-resistant Gram-negative bacteria.

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See Comment page 132

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MCR-1: Fosfoetanolamin transferaz enzimi ve fosfoetanolamini lipid A'ya ekliyor

E.coli : Et *ve h*ayvanlarda %15-21, insanlarda %1

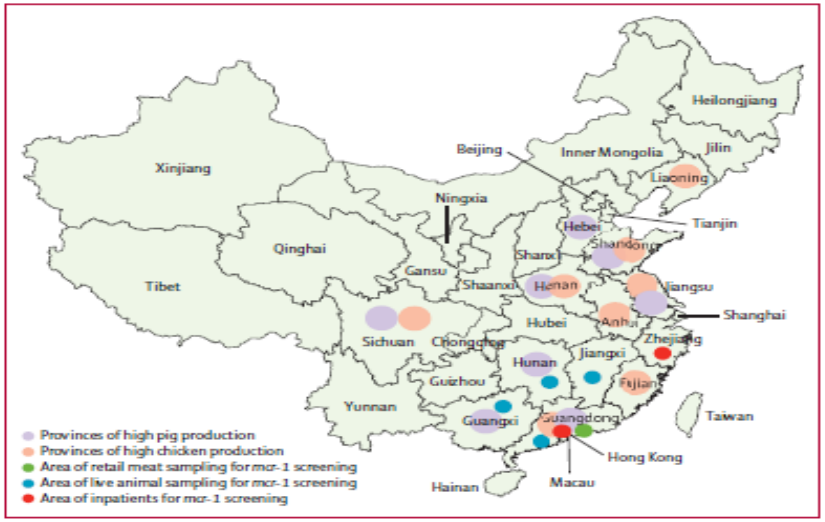

Figure 1: Map of China

	Origin	Polymyxin E (colistin)	Polymyxin B
Escherichia coli SHP45 (*mcr-1*)	Pig	8·0	4·0
E coli C600	..	0·5	0·5
E coli C600+ pHNSHP45 *mcr-1*)	Transconjugant	8·0	4·0
E coli E11 (ST131, KPC-2-producer)	Human	0·5	0·5
E coli E11 (ST131, KPC-2-producer) + pHNSHP45 (*mcr-1*)	Transformant	4·0	2·0
Klebsiella pneumoniae MPC11	Human	0·5	0·5
K pneumoniae MPC11 + pHNSHP45 (*mcr-1*)	Transformant	8·0	4·0
K pneumoniae 1202 (ST11, KPC-2-producer)	Human	0·5	0·5
K pneumoniae 1202 (ST11, KPC-2-producer) + pHNSHP45 (*mcr-1*)	Transformant	4·0	4·0
Pseudomonas aeruginosa HE26	Human	0·5	0·5
P aeruginosa HE26 + pHNSHP45(*mcr-1*)	Transformant	8·0	4·0
E coli W3110+ pUC18	Laboratory strain	0·5	0·5
E coli W3110 + pUC18-*mcr-1*	Transformant	2·0	2·0

Table 1: Minimum inhibitory concentration (mg/L) for parental strain, transformants, and transconjugant

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

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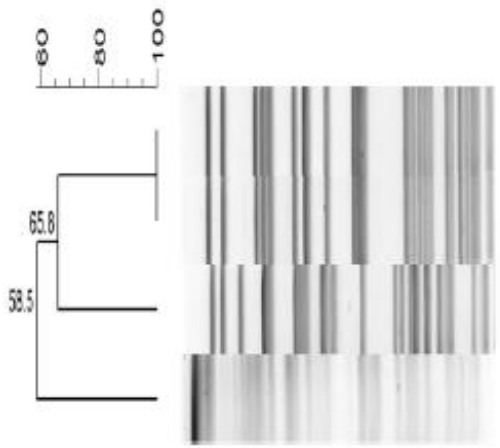

Strains (MLST type)	Antibiotic Resistance Profile	Resistance Genes
A1 (ST-3941)	PRL, TE, LEV, CIP, CT	bla_{TEM-1c}, *aph(3")-Ib*, *abh(6)-Id*, *floR*, *sul2*, *tetB*, *mcr-1*
A7 (ND)	PRL, TE, LEV, CIP, CT	ND
A9 (ST-1049)	PRL, FEP, ATM, CAZ, CT	$bla_{CTX-M-15}$, *mcr-1*
A5 (ST-3941)	PRL, TE, SXT, LEV, CIP, CT	bla_{TEM-1b}, *aadA5*, *aph(3")-Ib*, *abh(6)-Id*, *mphA*, *catA1*, *sul1*, *sul2*, *dfrA17*, *tetA*, *mcr-1*

Fig. 1. Pulsed-field gel electrophoresis (PFGE) profile and genetic characterisation of *mcr-1*-positive *Escherichia coli* isolates from chicken meat samples in Turkey. MLST, multilocus sequence typing; PIP, piperacillin; TET, tetracycline; LVX, levofloxacin; CIP, ciprofloxacin; COL, colistin; ND, not determined; FEP, cefepime; ATM, aztreonam; CAZ, ceftazidime; SXT, trimethoprim/sulfamethoxazole.

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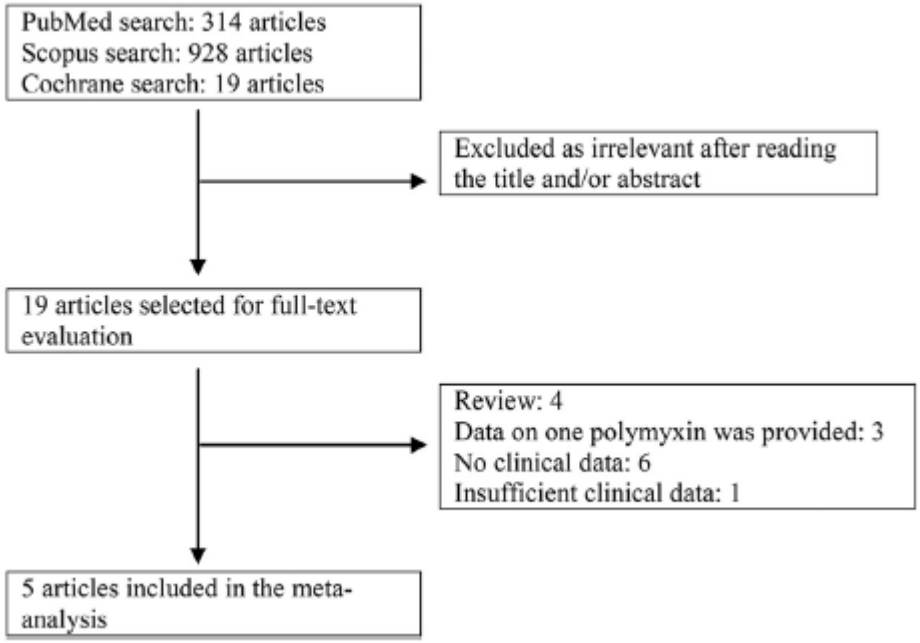
Colistin versus polymyxin B for the treatment of patients with multidrug-resistant Gram-negative infections: a systematic review and meta-analysis

Konstantinos Z. Vardakas [a,b], Matthew E. Falagas [a,b,c,*]



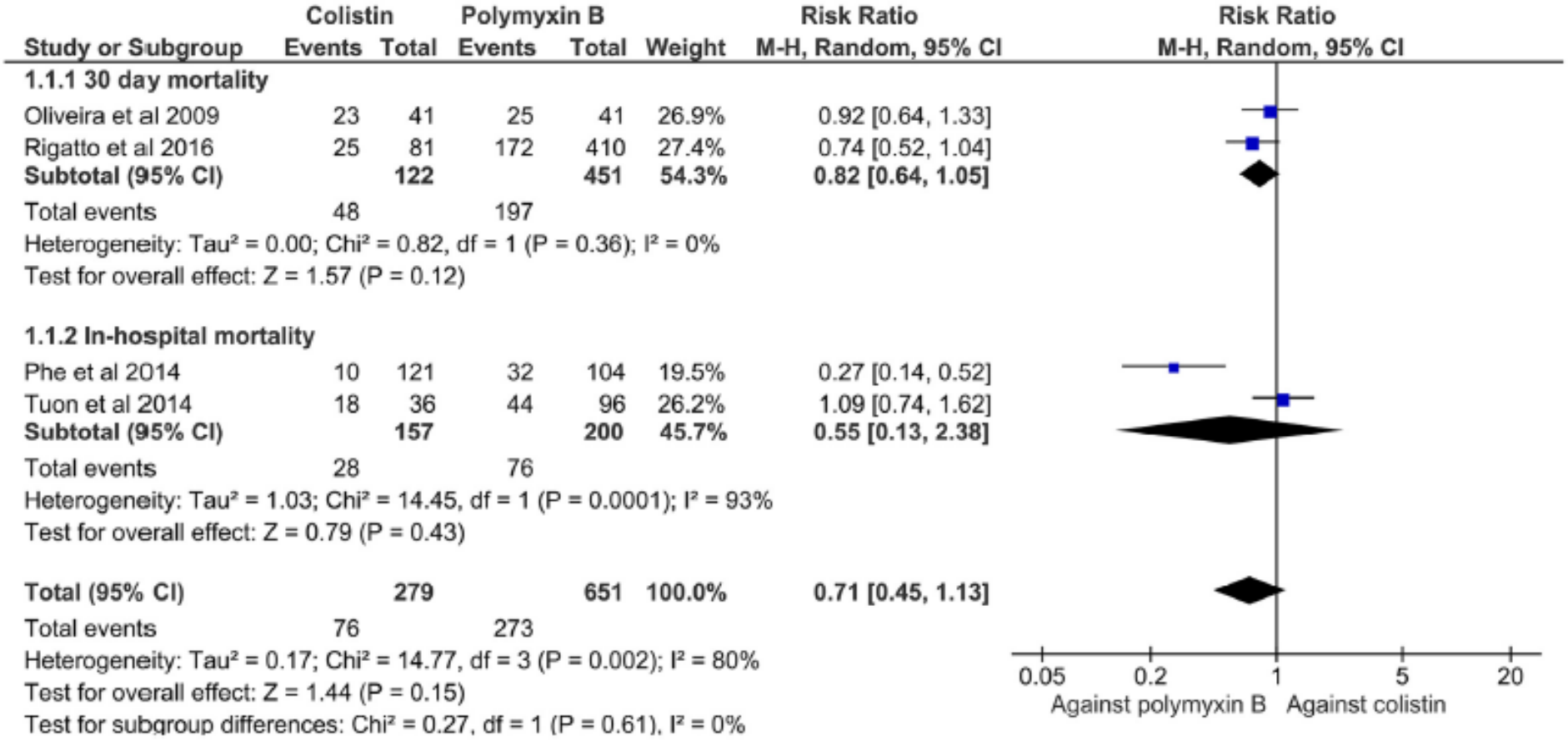


Fig. 2. Forest plots for mortality among colistin- and polymyxin B-treated patients. ■, risk ratio; –, 95% confidence interval (CI); ◆, pooled risk ratio.

Study or Subgroup	Colistin Events	Colistin Total	Polymyxin B Events	Polymyxin B Total	Weight	Risk Ratio M-H, Random, 95% CI
Akajagbor et al 2013	64	106	28	67	17.2%	1.44 [1.05, 1.99]
Oliveira et al 2009	10	39	8	30	2.8%	0.96 [0.43, 2.14]
Phe et al 2014	41	121	24	104	9.6%	1.47 [0.95, 2.26]
Rigatto et al 2016	60	81	189	410	64.8%	1.61 [1.36, 1.90]
Tuon et al 2014	14	36	20	96	5.6%	1.87 [1.06, 3.29]
Total (95% CI)		**383**		**707**	**100.0%**	**1.55 [1.36, 1.78]**
Total events	189		269			

Heterogeneity: Tau² = 0.00; Chi² = 2.31, df = 4 (P = 0.68); I² = 0%
Test for overall effect: Z = 6.47 (P < 0.00001)

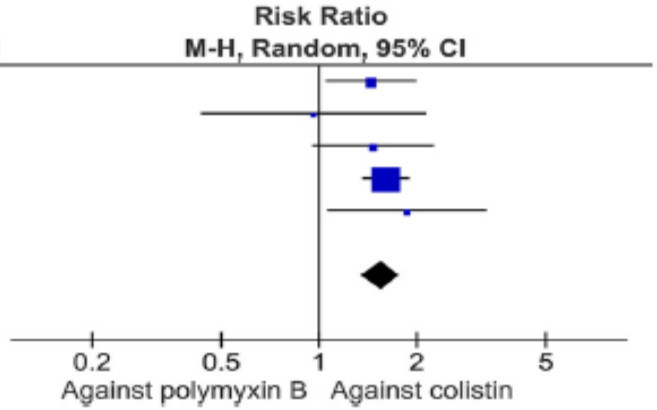


Fig. 3. Forest plots for unadjusted nephrotoxicity among colistin- and polymyxin B-treated patients. ■, risk ratio; ––, 95% confidence interval (CI); ◆, pooled risk ratio.

Study or Subgroup	log[Hazard Ratio]	SE	Colistin Total	Polymyxin B Total	Weight	Hazard Ratio IV, Random, 95% CI
Akajagbor et al 2013	0.82	0.27	106	67	29.1%	2.27 [1.34, 3.85]
Oliveira et al 2009	0	0.55	39	30	11.6%	1.00 [0.34, 2.94]
Rigatto et al 2016	1.21	0.25	81	410	31.2%	3.35 [2.05, 5.47]
Tuon et al 2014	0.55	0.28	36	96	28.1%	1.73 [1.00, 3.00]
Total (95% CI)			**262**	**603**	**100.0%**	**2.16 [1.43, 3.27]**

Heterogeneity: Tau² = 0.08; Chi² = 5.59, df = 3 (P = 0.13); I² = 46%
Test for overall effect: Z = 3.65 (P = 0.0003)

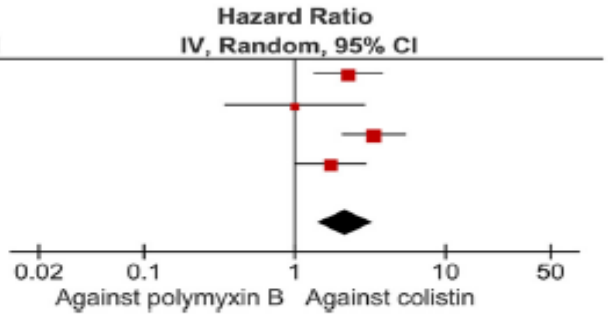


Fig. 4. Forest plots for adjusted nephrotoxicity among colistin- and polymyxin B-treated patients. ■, adjusted hazard ratio; ––, 95% confidence interval (CI); ◆, pooled hazard ratio.

Özet

- *A. baumannii* enfeksiyonlarında kolistin monoterapisi mortaliteyi artırmıyor
- *K. pneumoniae* enfeksiyonlarında kolistin içeren kombinasyon tedavisi mortaliteyi anlamlı azaltıyor
- VİP: Kolistinin İV tedaviye ek olarak inhalasyon şeklinde verilmesi için kanıtlar yeterli değil
- Menenjit: Erken ve intraventriküler
- Polimiksin-B daha az nefrotoksik