Gram-Negatifler İçin Eski ve Yeni Antibiyotikler

Prof. Dr. Halis Akalın

Eski Antibiyotikler

- Kolistin
- Aminoglikozidler
- Fosfomisin
- Tigesiklin

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

Hajo Grundmann, Corinna Glasner*, Barbara Albiger, David M Aanensen, Chris T Tomlinson, Arjana Tambić Andrasević, Rafael Cantón, Yehuda Carmeli, Alexander W Friedrich, Christian G Giske, Youri Glupczynski, Marek Gniadkowski, David M Livermore, Patrice Nordmann, Laurent Poirel, Gian M Rossolini, Harald Seifert, Alkiviadis Vatopoulos, Timothy Walsh, Neil Woodford, Dominique L Monnet, and the European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group†*

Summary

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

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

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

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

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

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

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

KPC(+) *K. pneumoniae* - Tedavi

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

Tumbarello M et al. Clin Infect Dis 2012

KPC(+) *K. pneumoniae* - Tedavi

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

Tumbarello M et al. J Antimicrob Chemother 2015

KD-*K.pneumoniae*

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

Kontopidou F et al. Clin Microbiol Infect 2013

OXA-48(+) Enterobacteriaceae

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

Balkan İİ et al. Int J Infect Dis 2014

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

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

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

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

Yüksek mortalite skoru olan hastalarda kombinasyon tedavisi

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

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

KDE – Polimiksin - Metaanaliz

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

KDE – Polimiksin - Metaanaliz

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

Ni W et al. Braz J Infect Dis 2015

KDE – Kombinasyon - Metaanaliz

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

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

KDE – Kombinasyon - Metaanaliz

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

Falagas ME et al. Antimicrob Agents Chemother 2014

Karbapenem Dirençli GNB

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

Zusman O et al. J Antimicrob Chemother 2017

Karbapenem Dirençli *Klebsiella pneumoniae*

- Çift Karbapenem Tedavisi
- Kolistin + Çift Karbapenem Tedavisi

KDKp
Ertapenem + Meropenem

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

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Journal of Antimicrobial Chemotherapy

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

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

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

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

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

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

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

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

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

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

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

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

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

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

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

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

(*Medicine* 95(11):e3126)

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

INTRODUCTION

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

NDM-1(+) KDKp

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

Berçot B et al. J Antimicrob Chemother 2011

Tigesiklin + Kolistin

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

Betts JW et al. Antimicrob Agents Chemother 2014

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

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

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

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

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

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

Fosfomisin - Kombinasyon

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

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Short Communication

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

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ABSTRACT

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

Fosfomisin + Amikasin en etkili kombinasyon

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Journal of Antimicrobial Chemotherapy

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

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

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

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

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

Kolistin + Fosfomisin Sinerjik

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

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ABSTRACT

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

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

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

Kolistin + Fosfomisin antagonistik

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

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ABSTRACT

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

Table 4
Patient outcomes in the effectiveness population ($n = 48$).[a]

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

CR-BSI, catheter-related bloodstream infection; VAP, ventilator-associated pneumonia; IAI, intra-abdominal infection; UIT, urinary tract infection.
[a] Data are no. (%) of patients.

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

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

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

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.

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

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G

S U M M A R Y

This article describes the emergence of resistance and predictors of fatality for 1556 cases of healthcare-associated Gram-negative bloodstream infection in 2014 and 2015. The colistin resistance rate in *Klebsiella pneumoniae* was 16.1%, compared with 6% in 2013. In total, 660 (42.4%) cases were fatal. The highest fatality rate was among patients with *Acinetobacter baumannii* bacteraemia (58%), followed by *Pseudomonas aeruginosa* (45%), *Klebsiella pneumoniae* (41%), *Enterobacter cloacae* (32%) and *Escherichia coli* (28%). On multi-variate analysis, the minimum inhibitory concentrations for carbapenems [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01–1.04; $P = 0.002$] and colistin (OR 1.1, 95% CI 1.03–1.17; $P = 0.001$) were found to be significantly associated with fatality.

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

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

The most common primary diagnosis in the study patients was cardiovascular disease, followed by solid organ and haematological malignancies (Table II). On univariate analysis, numerous factors were found to be associated with fatality (Table II). On multi-variate analysis, age >70 years, central-catheter-related infections, ventilator-associated pneumonia, APACHE II score, MIC of carbapenems and MIC of colistin were included as the independent variables. The MICs of carbapenems [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.01—1.04; $P = 0.002$] and colistin (OR 1.1, 95% CI 1.03—1.17, $P = 0.001$) were the only factors that were significantly associated with fatality. The logistic regression model predicted fatality with sensitivity of 74% (area under receiver operating characteristic curve was 74%).

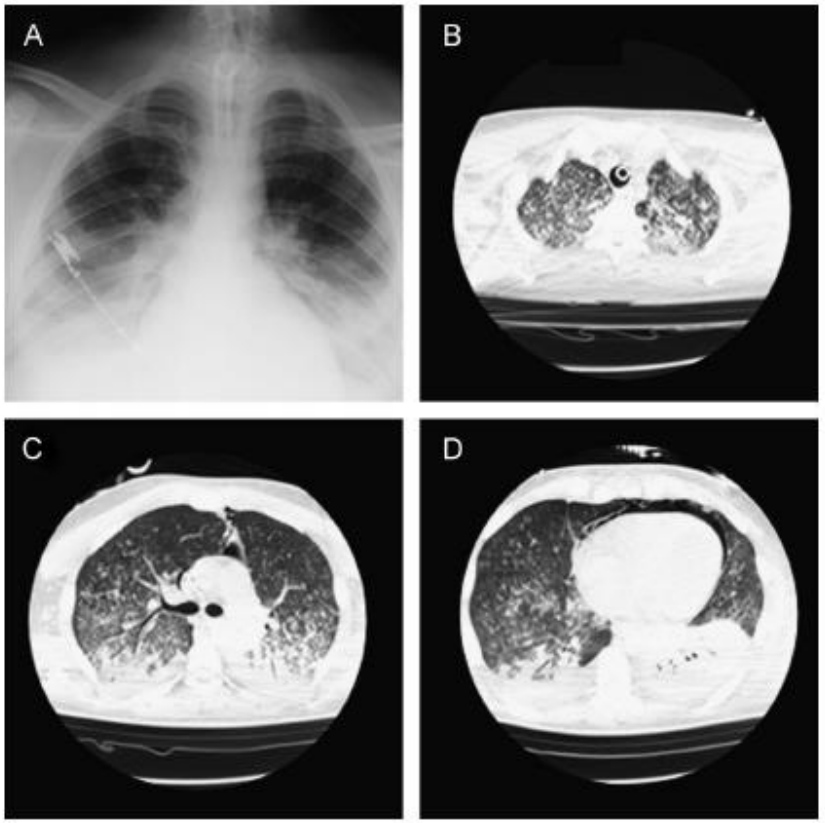
Kolistin Dirençli Kp - VİP

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

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

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

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



Kolistin Dirençli Kp - VİP

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

Viaggi B et al. Respir Invest 2015

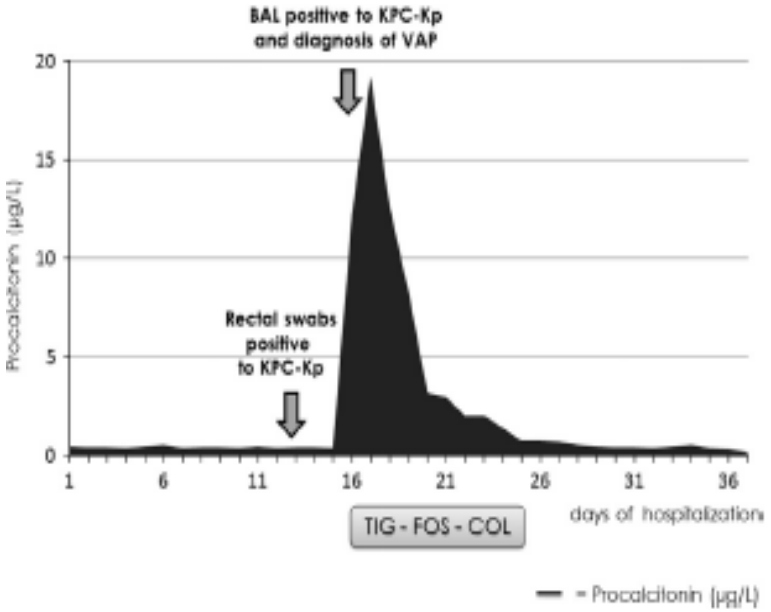


Fig. 2 – Time-course of serum procalcitonin concentration and antibiotic administrations in the intensive care unit. COL: colistin, FOS: fosfomycin, TIG: tigecycline, BAL: bronchoalveolar lavage, KPC-Kp: *Klebsiella pneumoniae* producing KPC-type carbapenemase.

Kolistin-R ve Karbapenem-R Kp

- Kolistin + Tigesiklin sinerjik

  Betts Jwet al. Antimicrob Agents Chemother 2014

- Kolistin + Ertapenem + Meropenem hızlı bakterisidal etki

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

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

International Journal of Antimicrobial Agents 51 (2018) 535–547

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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

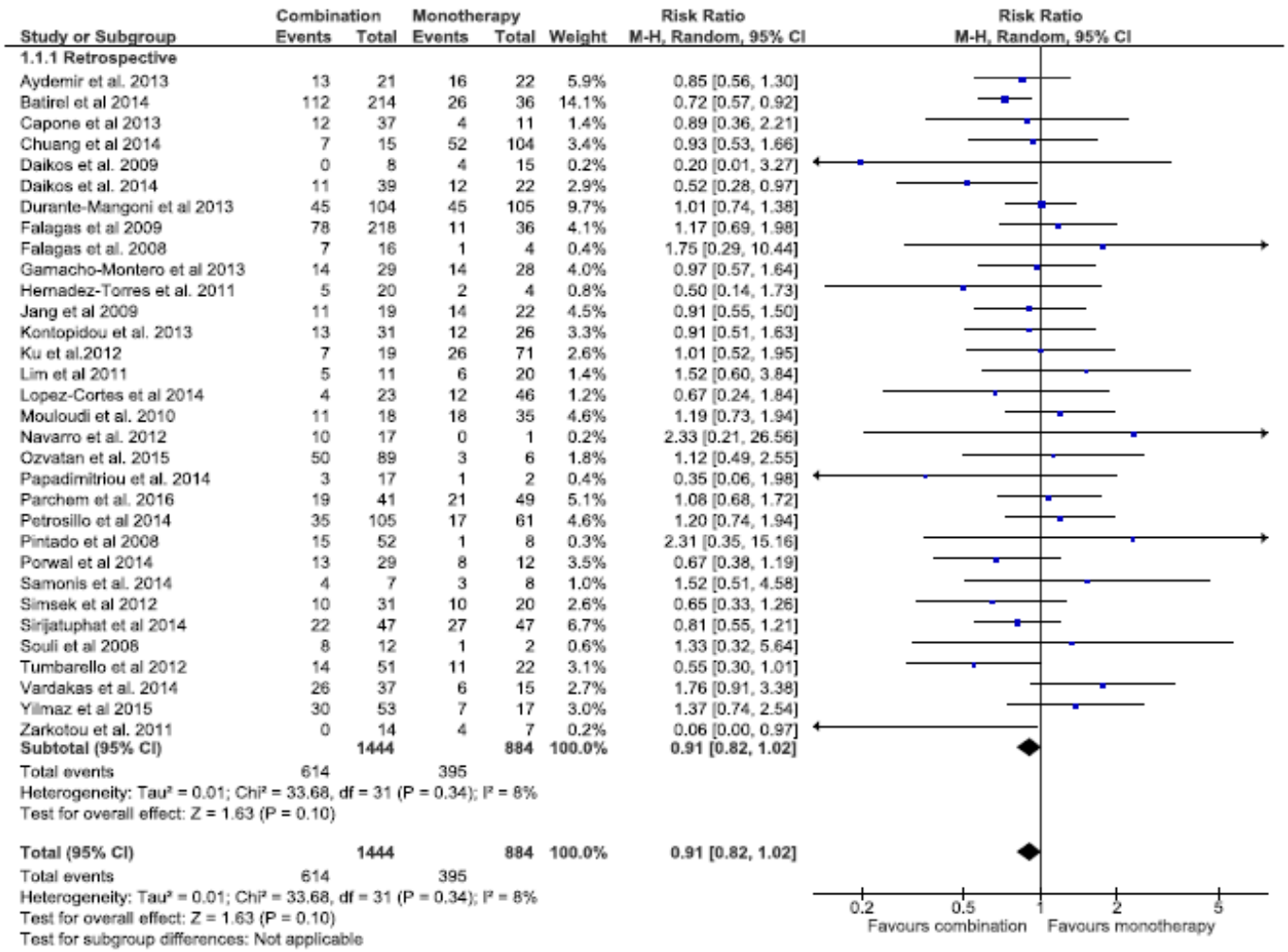

Fig. 2. Forest plot depicting the risk ratios of mortality among patients treated with intravenous colistin in combination with other antibiotics vs intravenous colistin monotherapy. Vertical line, 'no difference' point between the two regimens; squares, risk ratios; diamonds, pooled risk ratios for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

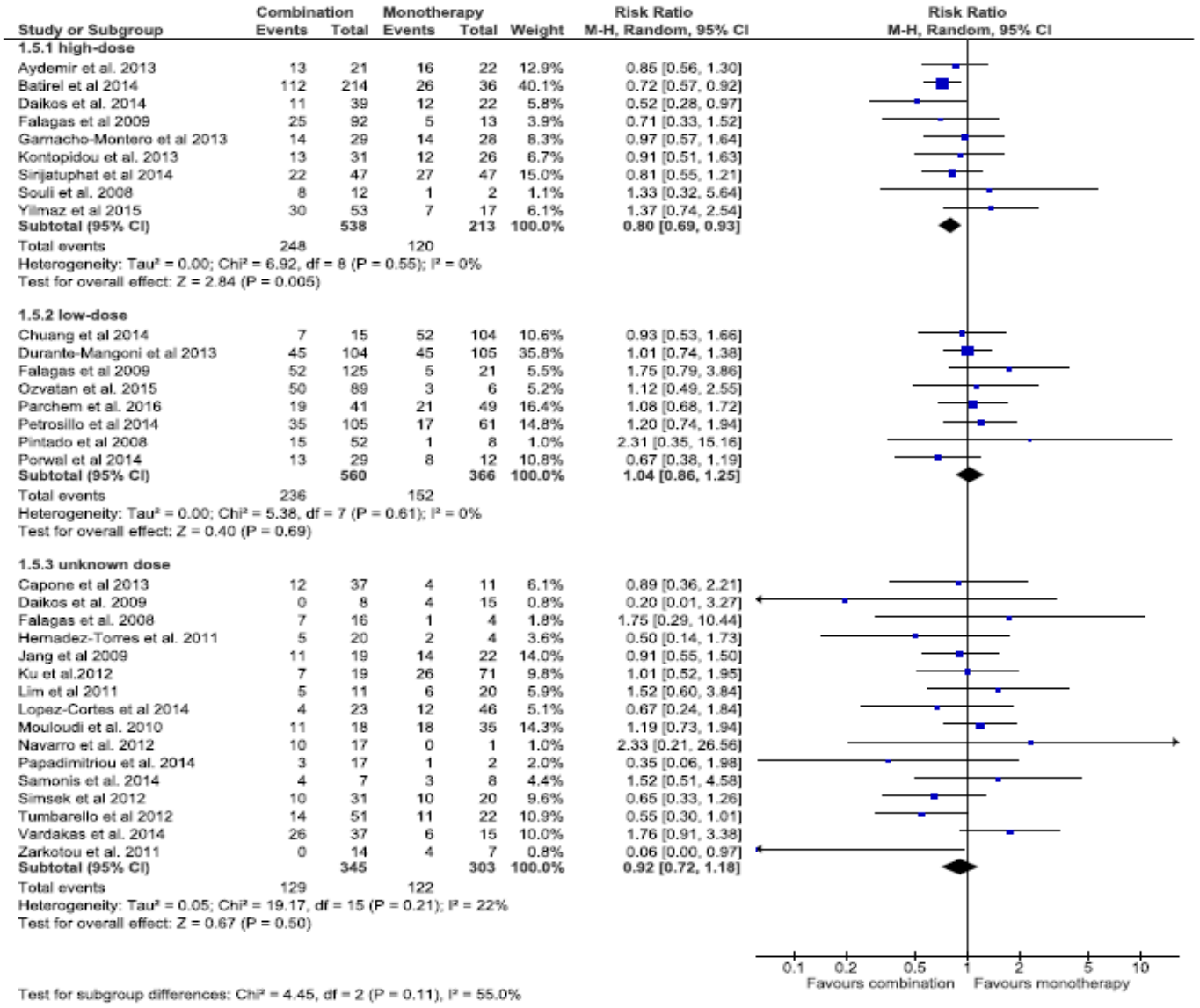

Fig. 3. Forest plot depicting the risk ratios of mortality among patients treated with intravenous colistin in combination with other antibiotics vs. intravenous colistin monotherapy according to colistin dose. Vertical line, 'no difference' point between the two regimens; squares, risk ratios; diamonds,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

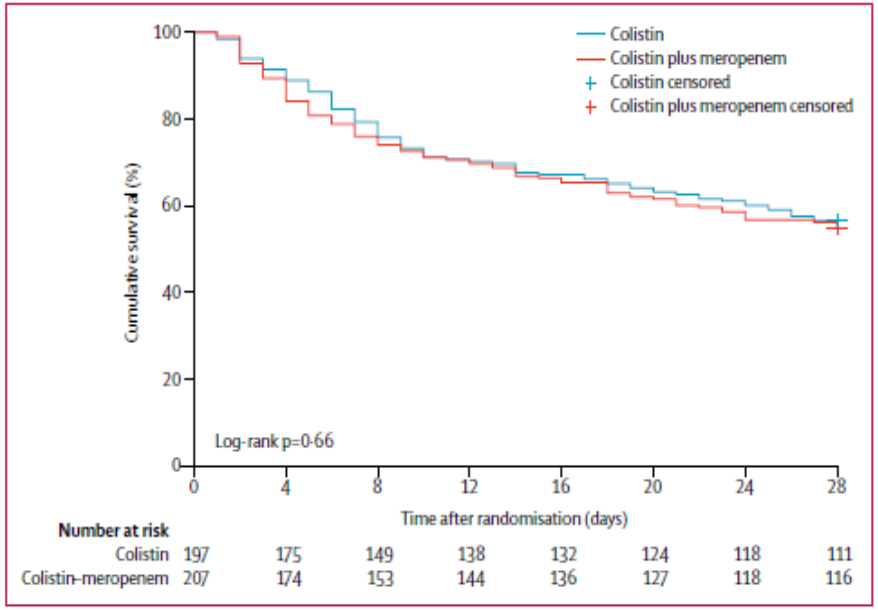

Figure 2: **Survival analysis to day 28 after randomisation**

	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?

Kolistin - İnhalasyon Tedavisi

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

Kofteridis DP et al. Clin Infect Dis 2010

Kolistin - İnhalasyon Tedavisi

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

Kofteridis DP et al. Clin Infect Dis 2010

Kolistin - İnhalasyon Tedavisi

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

Korbilla IP et al. Clin Microbiol Infect 2010

Kolistin - İnhalasyon Tedavisi

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

Korbilla IP et al. Clin Microbiol Infect 2010

Kolistin - İnhalasyon Tedavisi

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

Kalın G et al. J Infect Chemother 2012

Kolistin - İnhalasyon Tedavisi Meta-Analiz

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

Valachis A et al. Crit Care Med 2015

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

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Review

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

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Multidrug-resistant Gram-negative bacteria
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

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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

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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						

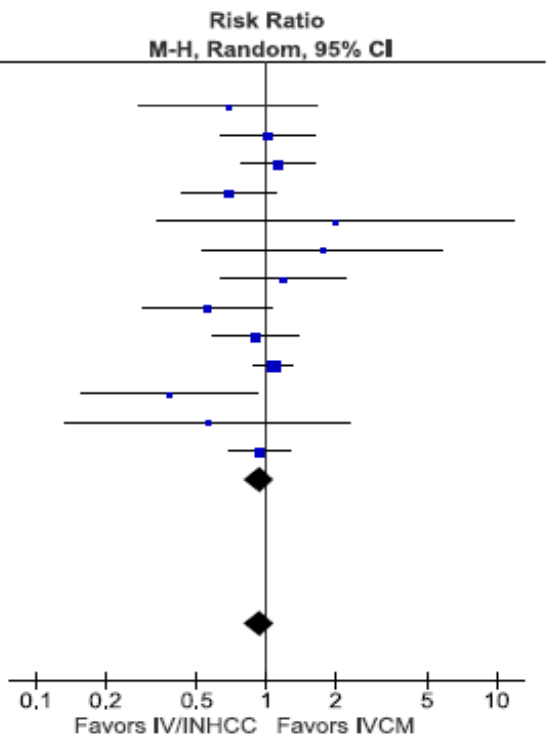

Fig. 2. Forest plot depicting the risk ratios (RR) of mortality among patients treated with IV/INHCC and IVCM. *(Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI. The areas of squares are proportional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

Tedavide Yeni Seçenekler

-Seftazidim/Avibaktam

-Seftarolin/Avibaktam

-Plazomisin

-Eravasiklin

-İmipenem/Relebaktam

-Meropenem/Vaborbaktam

-Aztreonam/Avibaktam

-Seftolozan/Tazobaktam

-Sefiderokol

The management of multidrug-resistant *Enterobacteriaceae*

Matteo Bassetti, Maddalena Peghin, and Davide Pecori

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

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

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

Seftolozan/Tazobaktam

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

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

Seftazidim/Avibaktam

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

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

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

Avibaktam

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

Aktaş Z et al. Int J Antimicrob Agents 2012

Aztreonam/Avibaktam

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

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

Clinical Infectious Diseases

MAJOR ARTICLE

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

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

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

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

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

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

İmipenem/Silastatin/Relebaktam

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

Thaden JT et al. Virulence 2016

Wright H et al. Clin Microbiol Infect 2017

Meropenem/Vaborbaktam

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

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

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

Plazomisin

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

Thaden JT et al. Virulence 2016
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Eravasiklin

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

Thaden JT et al. Virulence 2016
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Sefiderokol

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

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

Özet

- Karbapenem dirençli *A baumannii* için meta-analizler ve randomize kontrollü bir çalışma kolistin monoterapisini destekliyor
- Karbapenem dirençli *K pneumoniae* için kolistin + meropenem(yüksek doz, uzamış infüzyon ya da sürekli infüzyon)
- Karbapenem dirençli *K pneumoniae* için kolistin + fosfomisin veya AG veya tigesiklin
- Fosfomisin tek başına kullanılmamalı
- VİP tedavisinde İV tedaviye ek olarak kolistin inhalasyon tedavisi?

Özet

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