# Dirençli Gram-negatif Bakteri İnfeksiyonlarında Antibiyotik Tedavisi

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# Gram-negatif Bakterilerde Direnç

**Duyarlı**
**Gram-negatif patojenler**

**Dirençli *E.coli***
TEM
SHV Serin β-laktamazlar

**Dirençli *E.coli, P.aeruginosa*, *Klebsiella* spp.**
*AcrAB*
*blaSHV*
*blaTEM*
AmpC tipi β-laktamazlar

**Dirençli *E.coli, P.aeruginosa*, *Klebsiella* spp., *Enterobacter* spp. *Acinetobacter baumannii***
CTX-M 15
VIM
IMP
NDM-1
Porin defektleri

# ESKAPE

- ***E****nterococcus faecium*
- ***S****taphylococcus aureus*
- ***K****lebsiella pneumoniae*
- ***A****cinetobacter baumannii*
- ***P****seudomonas aeruginosa*
- ***E****nterobacter* spp.

Rice LB. J Infect Dis 2008; 197(8):1079-81.

# Yeni antibiyotik(ler) gerekli

- 3. derecede öncelikli: Orta

***Streptococcus pneumoniae***, penicillin-non-susceptible

***Haemophilus influenzae***, ampicillin-resistant

***Shigella*** *spp.*, fluoroquinolone-resistant

World Health Organization

# Yeni antibiyotik(ler) gerekli

- 2. derecede öncelikli :Yüksek

***Enterococcus faecium***, vancomycin-resistant

***Staphylococcus aureus***, methicillin-resistant, vancomycin intermediate and resistant

***Helicobacter pylori***, clarithromycin-resistant

***Campylobacter***, fluoroquinolone-resistant

***Salmonella*** *spp.*, fluoroquinolone-resistant

***Neisseria gonorrhoeae***, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

World Health Organization

# Yeni antibiyotik(ler) gerekli

- 1. derecede öncelikli: Kritik

***Acinetobacter baumannii***, carbapenem-resistant

***Pseudomonas aeruginosa***, carbapenem-resistant

***Enterobacteriaceae****, carbapenem-resistant, 3rd generation cephalosporin-resistant

World Health Organization

TABLE 7. *Pseudomonas aeruginosa*; examples of antimicrobial susceptibility profiles that fit MDR, XDR and PDR definitions; isolate no. 1 is PDR; isolate no. 2 is XDR and isolate no. 3 is MDR

| Antimicrobial category | Antimicrobial agent | Isolate no. 1 (PDR) | Isolate no. 2 (XDR) | Isolate no. 3 (MDR) |
|---|---|---|---|---|
| Aminoglycosides | Gentamicin | X[a] | X | |
| | Tobramycin | X | [b] | |
| | Amikacin | X | | |
| | Netilmicin | X | | |
| Antipseudomonal carbapenems | Imipenem | X | X | X |
| | Meropenem | X | X | |
| | Doripenem | X | X | |
| Antipseudomonal cephalosporins | Ceftazidime | X | | X |
| | Cefepime | X | X | |
| Antipseudomonal fluoroquinolones | Ciprofloxacin | X | X | X |
| | Levofloxacin | X | | |
| Antipseudomonal penicillins + $\beta$-lactamase inhibitors | Piperacillin-tazobactam | X | | |
| | Ticarcillin-clavulanic acid | X | X | |
| Monobactams | Aztreonam | X | X | |
| Phosphonic acids | Fosfomycin | X | | |
| Polymyxins | Colistin | X | | |
| | Polymyxin B | X | | |

Magiorakos et al. Clin Microbiol Infect 2012; 18:268-81.

# Sorun Nedir?

- Tedavi seçenekleri ?
- Maliyet
- Mortalite-morbidite

# Çözüm

- Kombinasyon stratejileri
  - Sinerji
- Farmakokinetik/farmakodinamik özellikler
- Eski antibiyotikler
- Antimikrobiyal yönetim

# Karbapenem Direnci

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

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

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

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

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

AAC
Journals.ASM.org

# Systematic Review and Meta-Analysis of *In Vitro* Synergy of Polymyxins and Carbapenems

Oren Zusman,[a] Tomer Avni,[a] Leonard Leibovici,[a] Amos Adler,[b] Lena Friberg,[c] Theodouli Stergiopoulou,[d] Yehuda Carmeli,[b] Mical Paul[e]

AAC 2013; 57 (10):5104-11.

- *A.baumannii, K.pneumoniae, P.aeruginosa*
- 39 makale, 15 bildiri
- 1054 izolat
- Checkerboard, Time-kill, E-test

| **Etken** | **Sinerji** |
|---|---|
| *A.baumannii* | %77 |
| *K.pneumoniae* | %44 |
| *P.aeruginosa* | %50 |

International Journal of Antimicrobial Agents 45 (2015) 8–18

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

Review

# In vitro synergy of polymyxins with other antibiotics for *Acinetobacter baumannii*: A systematic review and meta-analysis

Wentao Ni[a,1], Xiaodi Shao[b,1], Xiuzhen Di[b], Junchang Cui[a], Rui Wang[b], Youning Liu[a,*]

- Polimiksin duyarlı ve dirençli suşlar
  - Rifampisin, ampisilin-sulbaktam, sulbaktam, doripenem, imipenem, meropenem, tigesiklin, seftazidim, vankomisin, teikoplanin, linezolid, doksisiklin, levofloksasin tobramisin, seftobiprol, azitromisin
- Chequerboard, Time-kill, E-test
- 70 makale, 31 bildiri
- Polimiksin + karbapanem, polimiksin + glikopeptid sinerjik
- Karbapenem ve rifampisin ile kombinasyonlarında kolistin dirençli suşlarda sinerjik, kolistin direnci gelişimini önler

RESEARCH ARTICLE

# Activity of Colistin in Combination with Meropenem, Tigecycline, Fosfomycin, Fusidic Acid, Rifampin or Sulbactam against Extensively Drug-Resistant *Acinetobacter baumannii* in a Murine Thigh-Infection Model

PLOS One 2016;

Bing Fan[1,2☯], Jie Guan[3☯], Xiumei Wang[4], Yulong Cong[1]*

- Kolistin +

Meropenem
Tigesiklin
Sulbaktam
Rifampisin
Fusidik asit

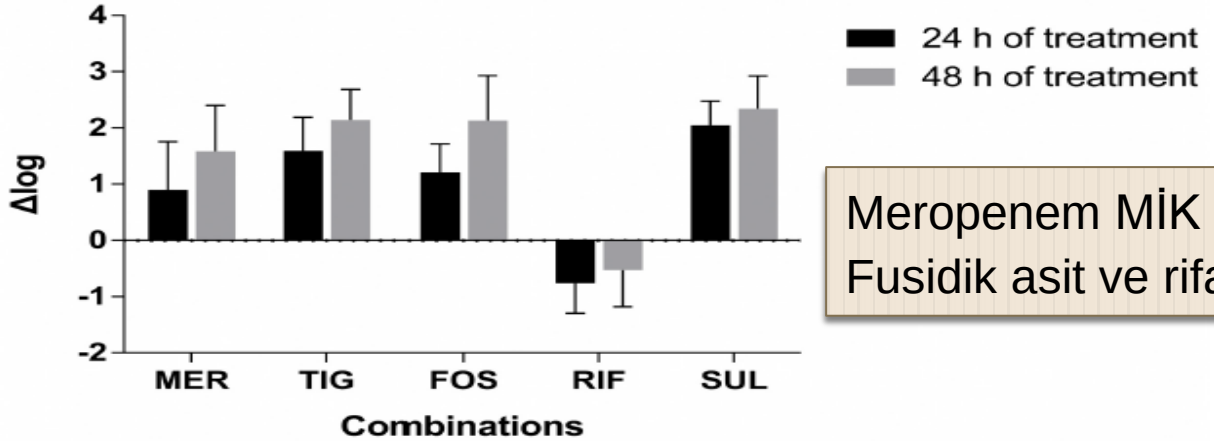


**Fig 2. Comparison of the efficacies of colistin-fusidic acid combination vs other combinations after 24 and 48 h of treatment.** CST, colistin; MER, meropenem; TIG, tigecycline; FOS, fosfomycin; FD, fusidic acid; RIF, rifampin; SUL, sulbactam. Δlog means the $\log_{10}$ recovered CFU of other combinations minus the $\log_{10}$ recovered CFU of colistin-fusidic acid combination.

Meropenem MİK ≤32 mg/L ise sinerji √
Fusidik asit ve rifampisin kombinasyonları √√

Eur J Clin Microbiol Infect Dis (2014) 33:1311–1322
DOI 10.1007/s10096-014-2070-6

ARTICLE

# Comparison of colistin–carbapenem, colistin–sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant *Acinetobacter baumannii* bloodstream infections

A. Batirel · I. I. Balkan · O. Karabay · C. Agalar · S. Akalin · O. Alici · E. Alp · F. A. Altay · N. Altin · F. Arslan · T. Aslan · N. Bekiroglu · S. Cesur · A. D. Celik · M. Dogan · B. Durdu · F. Duygu · A. Engin · D. O. Engin · I. Gonen · E. Guclu · T. Guven · C. A. Hatipoglu · S. Hosoglu · M. K. Karahocagil · A. U. Kilic · B. Ormen · D. Ozdemir · S. Ozer · N. Oztoprak · N. Sezak · V. Turhan · N. Turker · H. Yilmaz

- 27 merkez, retrospektif
- XDR-*A.baumannii* kan dolaşımı infeksiyonu

- Kolistin monoterapisi (37 olgu)

- Kolistin+karbapenem (102 olgu)
- Kolistin + sulbaktam (69 olgu
- Kolistin + diğer atb. (24'ü tigesiklin, toplam 43 olgu)
- Primer sonlanım 14. günlük sağkalım

Eur J Clin Microbiol Infect Dis (2014) 33:1311–1322
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ARTICLE

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| | Kombine | Monoterapi |
|---|---|---|
| | **214 (%)** | **36 (%)** |
| • 14 gün sağkalım | 146 (68.2) | 20 (55.5) |
| • Tam yanıt/kür | 99 (46.3) | 11 (30.6) |
| • Kısmi yanıt | 68 (31.8) | 16 (44.4) |
| • Yanıtsız | 47 (22) | 9 (25) |
| Mikrobiyolojik eradikasyon | 171 (79.9) | 20 (55.6) |

| | Kol+KAR | Kol+SUL | Kol+ATB |
|---|---|---|---|
| | **102 (%)** | **69 (%)** | **43 (%)** |
| 14 gün sağkalım | 72 (70.6) | 47 (68.1) | 27 (62.8) |
| Tam yanıt/kür | 50 (49) | 32 (46.4) | 17 (39.5) |
| Kısmi yanıt | 28 (27.5) | 23 (33.3) | 17 (39.5) |
| Yanıtsız | 24 (23.5) | 14 (17.4) | 9 (21) |
| Eradikasyon | 77/95(81) | 49/62(79) | 32/39(82) |

# Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

Clinical Infectious Diseases 2013;57(3):349–58

Emanuele Durante-Mangoni,[1] Giuseppe Signoriello,[2] Roberto Andini,[1] Annunziata Mattei,[3] Maria De Cristoforo,[4] Patrizia Murino,[3] Matteo Bassetti,[5,a] Paolo Malacarne,[6] Nicola Petrosillo,[7] Nicola Galdieri,[3] Paola Mocavero,[3] Antonio Corcione,[3] Claudio Viscoli,[5] Raffaele Zarrilli,[8] Ciro Gallo,[2] and Riccardo Utili[1]

- 5 merkez, randomize açık etiketli
- YBÜ'de yatan ve hayatı tehdit eden XDR *A.baumannii* infeksiyonu olan 210 olgu
  - Kolistin (3x2MU/gün)
  - Kolistin (3x2 MU/gün) + Rifampisin (2x600 mg i.v)
- Primer sonlanım 30 günde mortalite

# Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

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| Rifampisin MİK | Tüm olgular | Kol+Rif | Kol |
|---|---|---|---|
| | 209(%) | 104 (%) | 105 (%) |
| ≤16 mg/L | 160 (76.2) | 78 (75) | 82 (78.1) |
| >16 mg/L | 43 (20.5) | 23 (22.1) | 20 (19.0) |

| Sonuç | Kol+Rif | Kol | *p* |
|---|---|---|---|
| | 104 (%) | 105 (%) | |
| 30 gün mortalite | | | |
| Evet | 45 (43.3) | 45 (42.9) | |
| Hayır | 59 (56.7) | 60 (57.1) | |
| 30 günde inf.ilişkili ölüm | | | |
| Evet | 22 (21.15) | 28 (26.6) | |
| Hayır | 23 (22.1) | 17 (16.2) | |
| *A.baumannii* eradikasyon | | | |
| **Evet** | **63 (60.6)** | **47 (44.8)** | **.034** |
| Hayır | 38 (36.5) | 54 (51.4) | |
| Kolistin direnci gelişmesi | 0 | 0 | |

# Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis

Kirati Kengkla[1], Khachen Kongpakwattana[2], Surasak Saokaew[1–3,6], Anucha Apisarnthanarak[4] and Nathorn Chaiyakunapruk[2,3,5,6]*

J Antimicrobial Chemother 2018; 73:22-32.

- PubMed, Embase, Cochrane
- 29 çalışma, 2529 hasta
- Kolistin + Sulbaktam + Tigesiklin en yüksek kür oranı, anlamlı değil
- Mortalite açısından kombinasyon tedavileri ile kolistin monoterapileri arasında fark yok
- Kolistin + Sulbaktam mikrobiyolojik kür daha yüksek

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,*]

Int J Antimicrobial Agents 2018; 51:535-47.

- Metaanaliz
  - 29 gözlemsel, 3 randomize (32 çalışma)
  - *A.baumannii*, *K.pneumoniae*
  - 2328 hasta
  - IV Kolistin Kombinasyon-IV Kolistin Monoterapi
  - Fark yok ancak
    - Yüksek kolistin dozları ile kombinasyonlarda mortalite daha az

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,*]

**Table 2**
Outcomes of sensitivity and subgroup analyses.

| Groups/subgroups | Studies (*n*) | Number of patients | Risk ratio M-H, random, (95% CI) | Heterogeneity and degree of he |
|---|---|---|---|---|
| Study design | | | | |
| Retrospective | 22 | 1722 | 0.95 (0.82–1.10) | $P = 0.18$, $I^2$ 22% |
| Prospective | 6 | 203 | 0.64 (0.35–1.16) | $P = 0.36$, $I^2$ 8% |
| RCTs | 3 | 346 | 0.91 (0.74–1.12) | $P = 0.66$, $I^2$ 0% |
| Retro-prospective | 1 | 57 | 0.91 (0.51–1.63) | Not applicable |
| Infection site | | | | |
| Respiratory tract | 7 | 515 | 0.99 (0.81–1.21) | $P = 0.92$, $I^2$ 0% |
| Bacteraemia | | | | $P = 0.15$, $I^2$ 31% |
| Multiple sites | | | | $P = 0.68$, $I^2$ 0% |
| Microbiology | | | | |
| *A. baumannii* | | | | $P = 0.73$, $I^2$ 0% |
| *K. pneumoniae* | | | | $P = 0.08$, $I^2$ 40% |
| Number of antibiotics in combination regimens | | | | |
| Two antibiotics | 23 | 1749 | 0.95 (0.84–1.09) | $P = 0.32$, $I^2$ 10% |
| + carbapenems | 11 | 657 | 0.88 (0.72–1.07) | $P = 0.79$, $I^2$ 0% |
| + tigecycline | 9 | 348 | 0.91 (0.58–1.42) | $P = 0.05$, $I^2$ 49% |
| + aminoglycosides | 9 | 269 | 1.20 (0.90–1.60) | $P = 0.71$, $I^2$ 0% |
| + non-carbapenem β-lactams | | | 1.52 (0.76–3.02) | $P < 0.001$, $I^2$ 82% |
| + fosfomycin | | | 0.80 (0.55–1.18) | $P = 0.61$, $I^2$ 0% |
| + rifampin | | | 0.96 (0.75–1.23) | $P = 0.70$, $I^2$ 0% |
| Three antibiotics | | | 0.84 (0.58–1.22) | $P = 0.46$, $I^2$0% |
| Dose | | | | |
| High | | | 0.80 (0.69–0.93) | $P = 0.55$, $I^2$0% |
| Low | | | 1.04 (0.86–1.25) | $P = 0.61$, $I^2$0% |
| Undefined | | | 0.92 (0.72–1.18) | $P = 0.21$, $I^2$22% |
| Definition of combination | | | | |
| Active | | | 1.19 (0.87–1.61) | $P = 0.88$, $I^2$0% |
| Active at study level | | | 0.83 (0.66–1.04) | $P = 0.19$, $I^2$26% |
| Inactive | | | 1.17 (0.74–1.85) | $P = 0.52$, $I^2$0% |
| Study period | | | | |
| Up to 2010 | | | 1.01 (0.83–1.21) | $P = 0.39$, $I^2$5% |
| After 2010 | | | 0.90 (0.62–1.31) | $P = 0.22$, $I^2$34% |
| Study periods overlap | | | 0.86 (0.74–1.00) | $P = 0.37$, $I^2$8% |
| Geographical area | | | | |
| Europe | | | 0.96 (0.80–1.16) | $P = 0.24$, $I^2$17% |
| Asia | 10 | 835 | 0.82 (0.71–0.95) | $P = 0.58$, $I^2$0% |
| USA | 2 | 180 | 1.06 (0.72–1.54) | $P = 0.86$, $I^2$0% |
| Study scope | | | | |
| Similar to meta-analysis | 15 | 1581 | 0.90 (0.79–1.02) | $P = 0.38$, $I^2$6% |
| Not similar to meta-analysis | 17 | 747 | 0.93 (0.74–1.17) | $P = 0.28$, $I^2$15% |
| Mortality time point | | | | |
| 7- and 10-day | 2 | 65 | 0.71 (0.34–1.48) | $P = 0.31$, $I^2$2% |
| 14-day | 4 | 420 | 0.82 (0.61–1.12) | $P = 0.46$, $I^2$0% |
| 28-/30-day | 13 | 1077 | 0.89 (0.74–1.06) | $P = 0.28$, $I^2$16% |
| Mortality setting | | | | |
| In-hospital | 11 | 1060 | 0.88 (0.77–1.02) | $P = 0.55$, $I^2$0% |
| ICU | 4 | 203 | 1.06 (0.77–1.45) | $P = 0.33$, $I^2$13% |
| Infection-related | 10 | 596 | 0.77 (0.58–1.02) | $P = 0.53$, $I^2$0% |
| MINORS score | | | | |
| ≤16 | 28 | 1958 | 0.93 (0.81–1.07) | $P = 0.23$, $I^2$16% |
| >16 | 1 | 24 | 0.50 (0.14–1.73) | Not applicable |

Genel olarak mortalite değişmiyor

Bakteriyemi
*A.baumannii*
Yüksek doz kolistin
Asya çalışmaları

# Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant

ed

Lancet Infect Dis 2018;
18: 391–400

Skiada, Roberto Andini,
in, Ioannis Pavleas,
W Mouton,

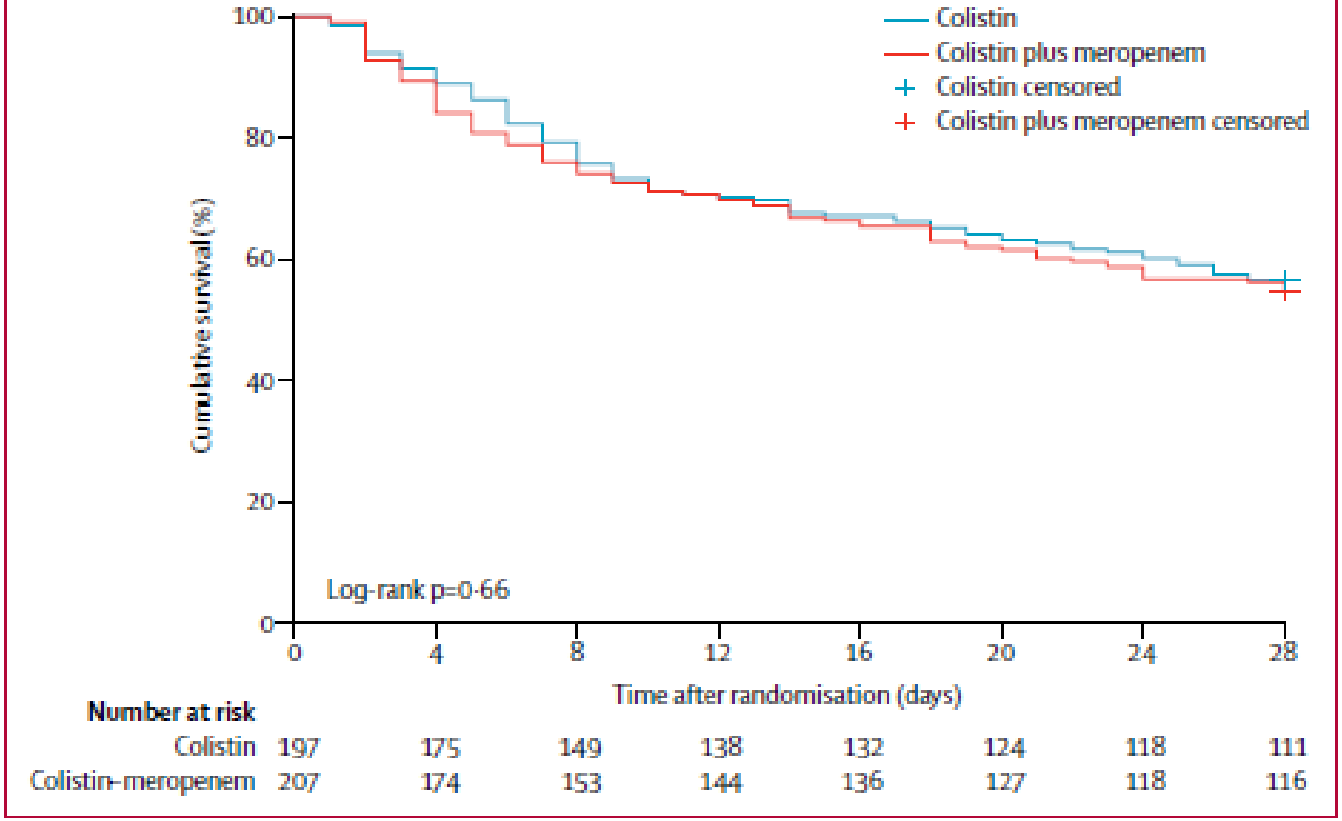


*Figure 2:* Survival analysis to day 28 after randomisation

mış infüzyon)

ombinasyon kolunda diyare
27-%16

| **Kolistin monoterapi** | | **Kombinasyon** |
|---|---|---|
| 156/198 | 14 günlük klinik başarısızlık | 152/208 |
| (%79) | 28 günlük mortalite | (%73) |
| %43 | Meropenem MİK | %45 |
| >8 mg/L (%97) | | >8 mg/L (%97) |

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

# *In Vitro* Synergistic Activity of Antimicrobial Agents in Combination against Clinical Isolates of Colistin-Resistant *Acinetobacter baumannii*

**Seongman Bae,[a] Min-Chul Kim,[a] Su-Jin Park,[a] Hee Sueng Kim,[a] Heungsup Sung,[b] Mi-Na Kim,[b] Sung-Han Kim,[a] Sang-Oh Lee,[a] Sang-Ho Choi,[a] Jun Hee Woo,[a] Yang Soo Kim,[a] Yong Pil Chong[a]**

Department of Infectious Diseases[a] and Department of Laboratory Medicine,[b] Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

- 9 klinik izolat (8 bakteriyemi, 1 pnömoni)
  - 9 kolistin dirençli
  - 6 PDR
  - 3 XDR
- Checkerboard yöntemi

**TABLE 1** The MIC values of antimicrobial agents against colistin-resistant *Acinetobacter baumannii* strains[a]

| Strain | MIC (μg/ml)[a] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CST | SAM | TGC | AMK | AZM | ATM | CAZ | MEM | RIF | SXT | VAN | TEC |
| a | 256 | 64/32 | 8 | 1,024 | >128 | 64 | 128 | 64 | 4 | 64/1,216 | 256 | 512 |
| b | 256 | 64/32 | 4 | 1,024 | >128 | 128 | 128 | 64 | 8 | 32/608 | 512 | 256 |
| c | 16 | 64/32 | 4 | 4 | 4 | 128 | 64 | 64 | 8 | 32/608 | 256 | 256 |
| d | 1,024 | 32/16 | 4 | >4,096 | >128 | 64 | 128 | 64 | 4 | 32/608 | 512 | 256 |
| e | 8 | 32/16 | 32 | 8 | 32 | 64 | 512 | 64 | 8 | 2/38 | 512 | 512 |
| f | 64 | 1,024/512 | 16 | 1,024 | >128 | 1,024 | 64 | 256 | 16 | 32/608 | 512 | 256 |
| g | 16 | 32/16 | 32 | 1,024 | >128 | 64 | 64 | 64 | 8 | 128/2,432 | 512 | 128 |
| h | 8 | 16/8 | 4 | 4 | >128 | 64 | 128 | 32 | 8 | 2/38 | 256 | 128 |
| i | 1,024 | 128/64 | 4 | 512 | >128 | 128 | 128 | 64 | 256 | 32/608 | 256 | 128 |

[a] Abbreviations: CST, colistin; SAM, ampicillin-sulbactam; TGC, tigecycline; AMK, amikacin; AZM, azithromycin; ATM, aztreonam; CAZ, ceftazidime; MEM, meropenem; RIF, rifampin; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin; TEC, teicoplanin.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

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Seongman Ba ng-Oh Lee,[a]
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TABLE 2 Combined effects of 12 antimicrobial drugs on nine colistin-resistant *A. baumannii* strains in the multiple-combination bactericidal test

| Agents[a] | Strain(s) killed[b] |
|---|---|
| SAM + RIF | e |
| SAM + SXT | f |
| SAM + TEC | d |
| AMK + CAZ | f |
| AMK + SXT | f |
| AZM + CAZ | f |
| AZM + SXT | f |
| AZM + TEC | e |
| ATM + CAZ | g |
| ATM + SXT | f |
| ATM + TEC | e |
| CAZ + MEM | f |
| CAZ + RIF | f |
| CAZ + TGC | f |
| CAZ + SXT | f |
| CAZ + VAN | f |
| MEM + RIF | h |
| MEM + SXT | f |
| MEM + TEC | e |
| RIF + SXT | f |
| SXT + VAN | f |
| AMK + RIF | a,f |
| CAZ + TEC | e,f |
| CST + AZM | b, d, e, h |
| CST + AMK | b, d, f, g |
| CST + SXT | b, d, f, h |
| CST + SAM | b, c, d, e, g |
| CST + CAZ | b, c, e, f, g, h |
| CST + ATM | a, b, c, d, e, g, h, i |
| CST + MEM | a, b, c, d, e, g, h, i |
| CST + VAN | a, b, c, d, e, g, h, i |
| CST + TEC | a, b, c, d, e, f, g, h, i (all) |
| CST + RIF | a, b, c, d, e, f, g, h, i (all) |

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

# *In Vitro* Synergistic Activity of Antimicrobial Agents in Combination against Clinical Isolates of Colistin-Resistant *Acinetobacter baumannii*

**Seongman Bae,[a] Min-Chul Kim,[a] Su-Jin Park,[a] Hee Sueng Kim,[a] Heungsup Sung,[b] Mi-Na Kim,[b] Sung-Han Kim,[a] Sang-Oh Lee,[a] Sang-Ho Choi,[a] Jun Hee Woo,[a] Yang Soo Kim,[a] Yong Pil Chong[a]**

Department of Infectious Diseases[a] and Department of Laboratory Medicine,[b] Asan Medical Center, University

14 günlük mortalite %67

TABLE 4 Clinical characteristics and treatment outcomes of patients with colistin-resistant *A. baumannii* infection[a]

| | Result(s) for patient: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | a | b | c | d | e | f | g | h | i |
| Age (yr)/gender | 61/M | 33/M | 66/M | 51/F | 82/M | 43/F | 51/M | 69/F | 67/F |
| Underlying disease | CBD cancer | LT | Hepatocellular carcinoma | Fulminant hepatitis due to HBV flare-up | Colon cancer, pelvic abscess | Myelodysplastic syndrome on BMT | LT | Metastatic CBD cancer | Supraglottic cancer |
| Acquisition | Hospital onset | Hospital onset | Hospital onset | Hospital onset | Hospital onset | Hospital onset | Hospital onset | Hospital onset | Hospital onset |
| Ward | SICU | SICU | SICU | MICU | SICU | BMT unit | LT unit | General ward | MICU |
| Type of infection | VAP, bacteremia | cIAI, bacteremia | cIAI, bacteremia | HAP, bacteremia | HAP, bacteremia | primary bacteremia | primary bacteremia | HAP, bacteremia | VAP |
| Clinical status | | | | | | | | | |
| Previous use of colistin | Yes | Yes | No | No | No | No | No | Yes | Yes |
| Previous use of carbapenem | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Recent operation | Yes | Yes | Yes | No | Yes | No | Yes | No | Yes |
| Antibiotic therapy | Colistin, vancomycin, amikacin | Colistin, meropenem, vancomycin | Colistin, vancomycin | Meropenem, vancomycin, levofloxacin | Meropenem, vancomycin, metronidazole | Imipenem, vancomycin, levofloxacin | Linezolid, levofloxacin | Tigecycline | Tigecycline, teicoplanin, rifampin, ampicillin-sulbactam |
| Microbiological eradication | Yes | No | Yes | No | No | No | Yes | No | No |
| Mortality | | | | | | | | | |
| 14 day | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No |
| 28 day | Yes | No | Yes | Yes | Yes | Yes | No | Yes | No |
| In hospital | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No |
| Infection related | No | No | No | Yes | Yes | Yes | No | Yes | No |

[a] Abbreviations: M, male; F, female; CBD, common bile duct; LT, liver transplantation; BMT, bone marrow transplantation; SICU, surgical intensive care unit; MICU, medical intensive care unit; VAP, ventilator-associated pneumonia; cIAI, complicated intra-abdominal infection; HAP, hospital-acquired pneumonia.

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# COMBINED THERAPY WITH IN VITRO SYNERGY FOR THE TREATMENT OF COLISTIN RESISTANT ENTEROBACTERIACEAE-KPC INFECTIONS

**S. De Gregorio**[1*], M. Nastro[2], N. Pozzi[1], C. Rodriguez[2], C. Vay[2], A. Famiglietti[2], D. Stecher[1], M. Foccoli[1]

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## Introduction and Objective

Antimicrobial treatment of KPC-producing *Enterobacteriaceae* isolates has not been well established yet. One proposed strategy is the use of combined antibiotic therapy.

**Objective**

To analyze the clinical outcome of patients with colistin-resistant- KPC-producing *K. pneumoniae* infection (CR-KPC-Kpi) treated with combined antimicrobial therapy with confirmed *in vitro* synergy.

## Materials and Methods

Study: retrospective and observational.

Data was extracted from inpatients' medical charts with CR-KPC-Kpi (MIC ≥ 4 µg/ml, EUCAST) at a university hospital from January 2010 to October 2013.

We evaluated age, sex, focus of infection, treatment and mortality at 28 days.

Definitions of focus of infection: according to CDC criteria

*In vitro* synergy was evaluated by killing curves or by comparing MIC/MBC values with and without a sub-inhibitory concentration of the antimicrobial used as synergistic.

## Results

Nineteen episodes of CR-KPC-Kpi were analyzed. Mean age: 57 years, 11 were men. Two patients received synergistic combination therapy and infectious focus wasn't removed and all of them died.

In next table we describe the outcome of 17 patients with adequate focus removal if necessary, and different antimicrobial treatments.

Synergistic associations were: a- colistin/rifampicin in all isolates, b- Other synergies: colistin/ piperacillin-tazobactam (1 isolate), colistin/ ciprofloxacin (1 isolate), colistin/ tigecycline (1isolate).

Fifteen patients were treated with antimicrobial combination and 33% died. All seven patients treated with *in vitro* synergistic antibiotics associations survived. Carbapenems MIC was ≥ 64 in 6/8 patients treated with colistin/carbapenems, 3 (37%) survived (lower UTI 2 and VAP 1).

## Results

| Infectious focus | CST MIC (µg/ml) | Cb MIC (µg/ml) | TGC MIC (µg/ml) | FOF MIC (µg/ml) | In vitro synergy | Result | Antibiotic treatment | Mortality 28 days | | Treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| Thorax SSI | 32 | 64 | 1 | 16 | CST-RIF | S | CST | Y | 100% (1/1) | Monotherapy resistant |
| Urological SSI | 16 | 64 | 1 | >64 | CST-RIF | S | TGC | N | 0% (0/1) | Monotherapy susceptible |
| Abdominal SSI | 64 | 64 | 1 | >64 | CST-RIF | S | CST + IPM | Y | 63% (5/8) | Combined therapy Colistin + carbapenem |
| Abdominal SSI | 4 | 64 | 1 | >64 | CST-RIF | S | CST + IPM | Y | | |
| Abdominal SSI | 64 | 64 | 1 | 32 | CST-RIF | S | CST + IPM | N | | |
| VAP | >64 | 64 | 1 | 32 | CST-RIF | S | CST + IPM | Y | | |
| BSI | 32 | 64 | 2 | 16 | CST-RIF | S | CST + IPM + FOF + TGC | Y | | |
| BSI | 8 | 64 | 2 | >64 | CST-RIF | S | CST + MEM | Y | | |
| Lower UTI | 4 | 8 | 2 | 16 | CST-RIF | S | CST + MEM | N | | |
| Lower UTI | 8 | ≤4 | 0.5 | — | CST-RIF | S | CST + MEM | N | | |
| Neurosurgical SSI | 32 | >16 | 1 | 8 | CST - RIF<br>CST-MEM<br>CST-CIPX<br>CST-TZP | S<br>S<br>S<br>S | CST + RIF + TGC | N | 0% (0/7) | Combined therapy with in vitro synergy |
| Abdominal SSI | 8 | 64 | 6 | 16 | CST-RIF | S | CST + RIF + MEM | N | | |
| HAP | 16 | 64 | 1 | 32 | CST-RIF | S | CST + RIF | N | | |
| CABSI | 16 | 64 | 1 | 16 | CST-RIF | S | CST + RIF + TGC | N | | |
| BSI | 64 | 16 | 1 | — | CST-RIF<br>CST-MEM<br>CST-TGC | S<br>S<br>S | CST + RIF + MEM<br>CST + TGC | N | | |
| Bacteriemic UTI | 8 | 64 | 2 | 8 | CST-RIF<br>CST-TGC | S<br>I | CST + RIF | N | | |
| Lower UTI | 32 | 8 | 1 | 16 | CST-RIF | S | CST + TGC<br>CST + RIF | N | | |

CST: colistin, Cb: carbapenems, IPM: imipenem, MEM: meropenem, FOF: fosfomycin, TGC: tigecycline, RIF: rifampicin, TZP: Piperacillin-tazobactam, CIPX: ciprofloxacin. SSI: surgical site infection, VAP: ventilator associated pneumonia, HAP: Hospital-acquired pneumonia, UTI: urinary tract infection, BSI: bloodstream infection, CABSI: catheter associated bloodstream infection. S: susceptible, I: intermediate.

## Conclusions

The best outcome was observed in patients treated with *in vitro* synergistic combined antimicrobial therapy. In this study colistin/ rifampicin was synergistic in all isolates. The removal of focus of infection was a basic requirement for survival when it was necessary.

## References

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2. Nastro M, Rodriguez C, Monge R, Zintgraff J, Neira L, Rebollo M, Vay C, Famiglietti A. Activity of the colistin-rifampicin combination against colistin-resistant, carbapenemase-producing Gram-negative bacteria. A. J Chemother. 2013 Dec 6:1973947813Y0000000136. [Epub ahead of print]

# SANFORD diyor ki…

- *A.baumannii* üremesi var, antibiyogram çıkıncaya kadar ampirik tedavi

  Direnç oranı <%10-15 ise

  - Monoterapi: Sefepim 3x2 gr i.v veya
    Meropenem 4x2 gr i.v (>30 dk. İnf) veya
    Meropenem 3x2 gr i.v (>3saat infüzyon) veya
    Meropenem 6 gr i.v (devamlı infüzyon) veya
    Amp.Sul. 4x3 gr i.v

  Direnç oranı ≥%10-15 ise

  Yukarıdaki ilaçlardan birisine ekle:

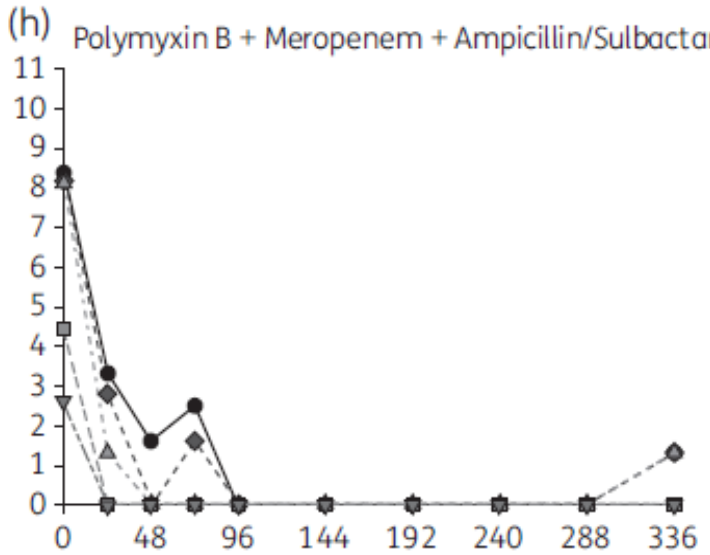
  Siprofloksasin 3x400 mg i.v veya
  Gentamisin veya tobramisin 7 mg/kg/gün i.v veya
  Polimiksin B 2.5 mg/kg i.v 2 saat inf, 12 saat sonra 1.5 mg/kg (1 saat inf), idame doz 12 saatte bir

# SANFORD

- *A.baumannii* tüm karbapenemlere dirençli ise:
  - Polimiksin B
  - Duyarlılık sonucuna göre aşağıdakilerden birisi eklenebilir
    - Minosiklin 200 mg i.v yükleme ardından 2x100 mg idame veya
    - Gentamisin veya tobramisin 7 mg/kg/gün i.v veya
    - Ampisilin-sulbaktam 4x3 gr i.v

# SANFORD

- Panrezistan *A.baumannii*
  - İnfeksiyon hastalıkları konsult
  - Konsultan yok ise kombinasy
  - Kolistin ve karbapenem dirençli ise:
  - Kolistin + Ampisilin-Sulbaktam + Karbapenem




*J Antimicrob Chemother* 2017; **72**: 1415–1420
doi:10.1093/jac/dkx002 Advance Access publication 28 February 2017

Journal of Antimicrobial Chemotherapy

**Polymyxin-resistant, carbapenem-resistant *Acinetobacter baumannii* is eradicated by a triple combination of agents that lack individual activity**

Lenhard JR et al.

Polimiksin dirençli, karbapenem dirençli, ampisilin-sulbaktam dirençli
PAP analizi
96.Saatte üçlü tedavi ile üreme yok
Polimiksin 3.3 mg/kg yükleme-1.43 mg/kg idame
Meropenem 2 gr 8 saat aralıklı, ampisilin sulbaktam 8/4 gr i.v 8 saat aralıklı

# 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,*]

J Infection 2018; 76:321-7.

13 çalışma
İnhaler tedavi eklenmesi mortaliteyi değiştirmemekte
Kolistin dozu düşük ise (<6MU/gün) inhaler tedavi ile mortalite daha az

# 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

Dong Liu [a], Jing Zhang [b], Hai-Xia Liu [a], Ying-Gang Zhu [a], Jie-Ming Qu [a,c,*]

Int J Antimicrobial Agents 2015; 46:603-9.

8 çalışma
İnhaler tedavi eklenmesi
mortaliteyi azaltmakta,
klinik yanıt oranları daha iyi,
mikrobiyolojik eradikasyon daha iyi

# Karbapanem dirençli Enterobacteriaceae

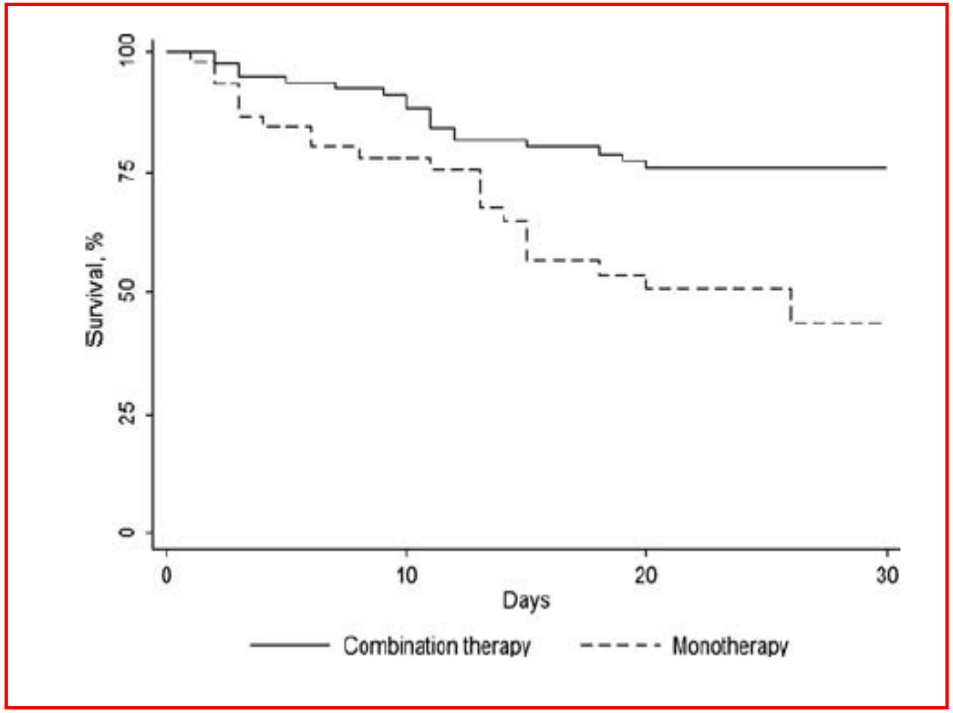
- Polimiksin + Karbapenemler
  - Sinerjik
  - Kolistin direnci gelişimin azaltmakta
- Meropenem 3x2 gr (MİK 2-8 mg/L ise)

# Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]

Clin Infect Dis 2012;55:943-50.

- Çok merkezli, retrospektif kohort
- 125 olgu: KPC (+) *K.pneumoniae* kan dolaşımı infeksiyonlu
- 30 günlük mortalite %41.6
- Monoterapi mortalite %54.3
  - Tigesiklin
  - Kolistin
  - Gentamisin
- **Kombinasyon mortalite %34.1 √**
  - Tigesiklin + kolistin
  - Tigesiklin + kolistin + meropenem
  - Tigesiklin + gentamisin
  - Kolistin + gentamisin
  - Tigesiklin + meropenem




Kolistin: 6-9 MU/gün
Meropenem 3x2 gr 3 saatlik infüzyon
Gentamisin: 5 mg/kg/gün
Tigesiklin: 100 mg/gün

# Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]

| Meropenem MİK (mg/L) | Toplam | Ölenler Sayı (%) | Sağkalanlar Sayı (%) |
|---|---|---|---|
| 1 | 1 | 0 | 1 (100) |
| 2 | 4 | 0 | 4 (100) |
| 4 | 10 | 2 (20) | 8 (80) |
| 8 | 4 | 1 (25) | 3 (75) |
| ≥16 | 17 | 6 (35.2) | 11 (64.7) |
| Toplam | 36 | 9 (25) | 27 (75) |

| Değişken | *p* | Odds |
|---|---|---|
| Septik şok | .008 | 7.17 |
| Başlangıç tedavisinin Uygunsuz olması | .004 | 4.17 |
| APACHE III skoru yüksek | <0.001 | 1.04 |
| Antibiyogram sonrasında **TİG + KOL + MER** | .01 | 0.11 |

Clin Infect Dis 2012;55:943-50

*J Antimicrob Chemother* 2015; **70**: 2133–2143
doi:10.1093/jac/dkv086 Advance Access publication 21 April 2015

Journal of Antimicrobial Chemotherapy

# Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

Mario Tumbarello[1]*, Enrico Maria Trecarichi[1], Francesco Giuseppe De Rosa[2,3], Maddalena Giannella[4], Daniele Roberto Giacobbe[5], Matteo Bassetti[6], Angela Raffaella Losito[1], Michele Bartoletti[4], Valerio Del Bono[5], Silvia Corcione[2,3], Giuseppe Maiuro[1], Sara Tedeschi[4], Luigi Celani[1], Chiara Simona Cardellino[2,3], Teresa Spanu[7], Anna Marchese[8], Simone Ambretti[9], Roberto Cauda[1], Claudio Viscoli[5] and Pierluigi Viale[4] on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

- Çok merkezli, retrospektif kohort
- 661 KPC (+) *K.pneumonia*e infeksiyonu olgusu
  - 447 olgu kan dolaşımı infeksiyonu
  - 214 olgu alt solunum yolu, intraabdominal, üriner sistem inf vs.
- 14 günlük mortalite 225/661 (%34.1)

| **Duyarlılıklar** | |
|---|---|
| Gentamisin | %82.1 |
| Kolistin | %80 |
| Tigesiklin | %77 |

*J Antimicrob Chemother* 2015; **70**: 2133–2143
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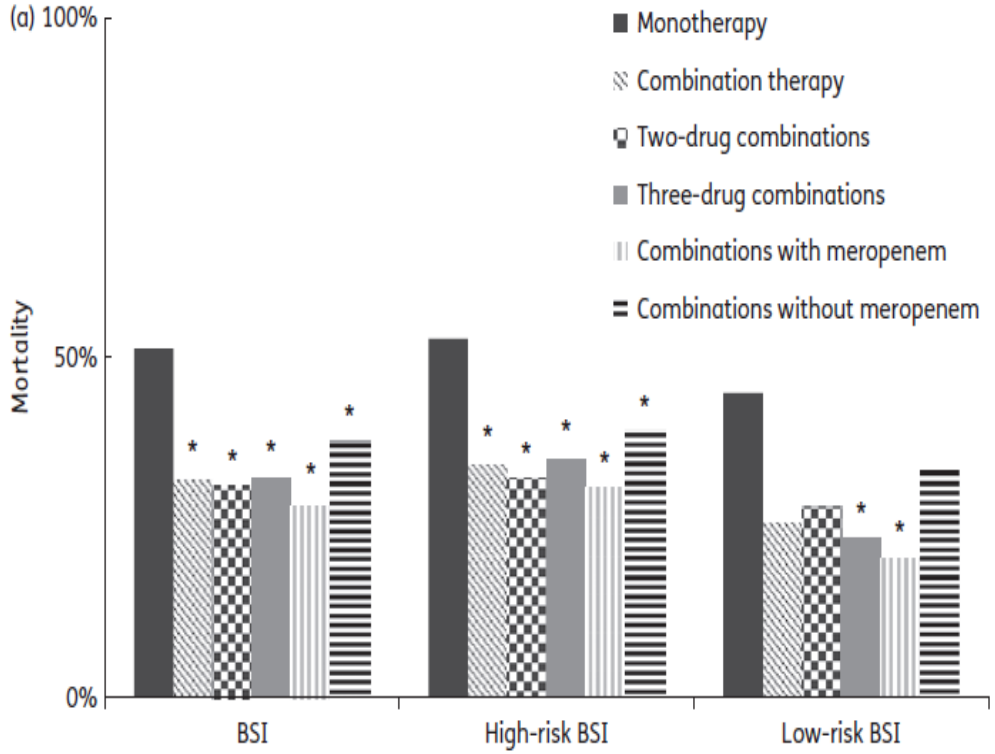


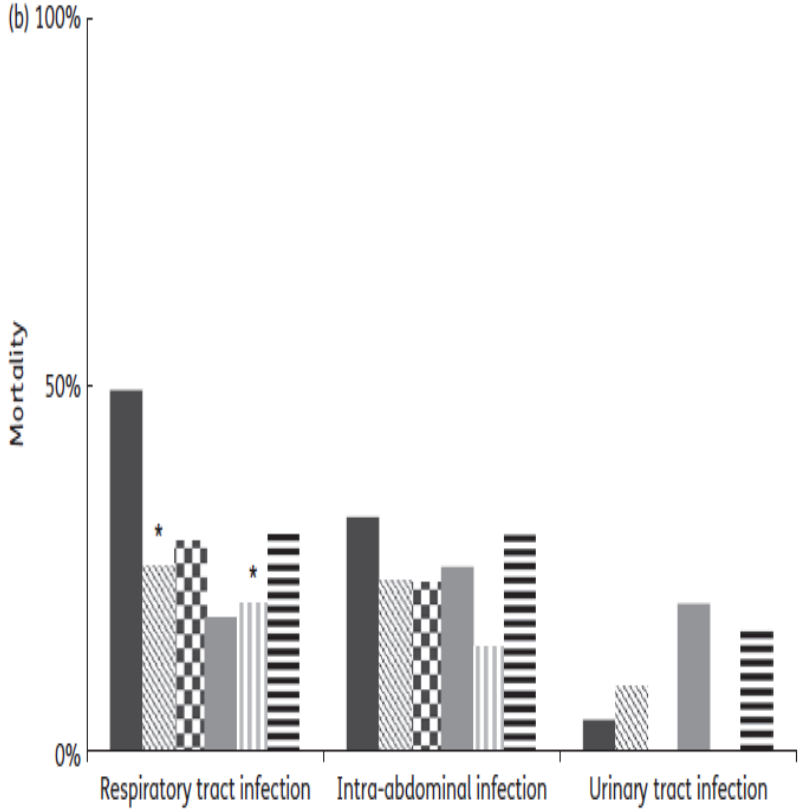

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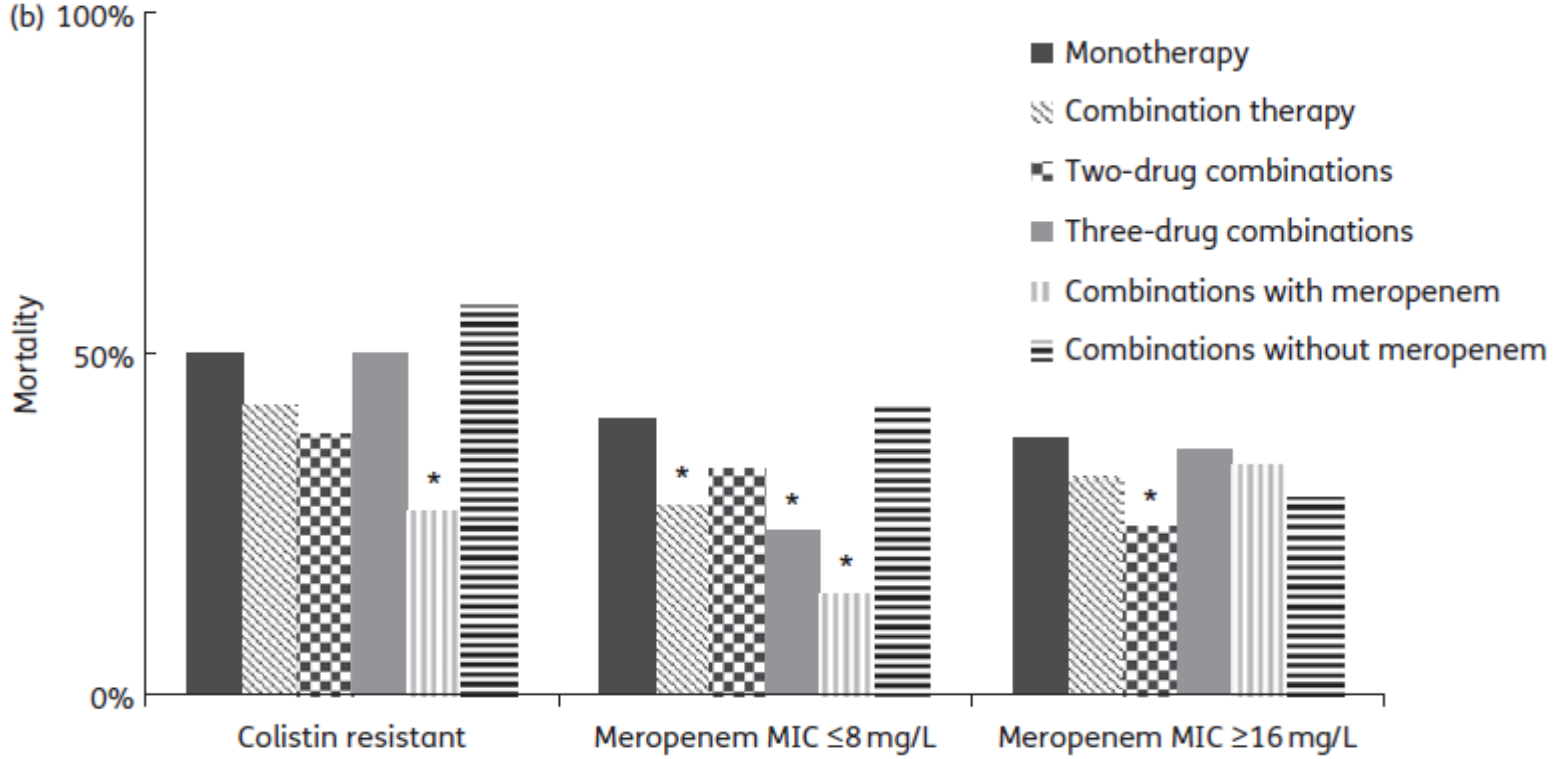

# Meropenem for treating KPC-producing Klebsiella pneumoniae bloodstream infections: Should we get to the PK/PD root of the paradox?

Valerio Del Bono, Daniele Roberto Giacobbe, Anna Marchese, Andrea Parisini, Carmen Fucile, Erika Coppo, Valeria Marini, Antonio Arena, Alexandre Molin, Antonietta Martelli, Angelo Gratarola, Claudio Viscoli, Paolo Pelosi & Francesca Mattioli

**ABSTRACT**

The objective of this study was to assess the achievement of pharmacokinetic/pharmacodynamic (PK/PD) targets of meropenem (MEM) in critically-ill patients with bloodstream infections (BSI) due to *Klebsiella pneumoniae*-carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp) with MEM minimum inhibitory concentrations (MICs) ≥16 mg/L. Nineteen critically-ill patients with KPC-Kp BSI were given combination therapy including MEM, tigecycline, plus colistin or gentamicin (according to susceptibility testing). MEM was administered as an extended 3-hour infusion of 2 g every 8 hours, or adjusted according to renal function. MEM plasma concentrations were determined by high-performance liquid chromatography. PK/PD targets for MEM were defined as T > 40% 1×MIC and T > 40% 4×MIC. Possible synergisms between MEM and coadministered agents were assessed by time-kill assays based on plasma levels for MEM and on fixed plasma concentrations for the other agents. In none of 19 patients MEM reached any PK/PD target. The actual MEM MICs were 256, 512, and 1024 mg/L in 1, 3, and 15 isolates, respectively. However, theoretically, the PK/PD target of T > 40% 1×MIC could have been achieved in 95%, 68%, 32% and 0% of the isolates for MIC equal to 8, 16, 32, and 64 mg/L, respectively. No synergisms were observed between MEM and coadministered agents. In conclusion, high-dose MEM failed to reach PK/PD targets in 19 patients with BSI due to KPC-Kp with very high MEM MICs. On a theoretical basis, our results suggest a possible usefulness of MEM against resistant blood isolates with MICs up to 32 mg/L.

# XDR/PDR

- Tascini ve ark.
- 13 kolistin dirençli KPC (+) *K.pneumoniae*
- Kolistin + rifampisin sinerjik

- Gonzalez-Padilla ve ark.
  - Retrospektif kohort
  - 50 sepsis olgusu: kolistin dirençli KPC (+) *K.pneumoniae*

  - Gentamisin ile kombine edildiğinde mortalite azalıyor %20.7-%61.9
  - Gentamisin MİK 2 mg/L

# Çift Karbapenem

- 8'i kan dolaşımı infeksiyonu olan 15 olgu
  - Ertapanem 1x1 gr + meropenem 3x2 gr infüzyon
  - Klinik/mikrobiyolojik yanıt %80
  - Sinerji
    - %78.6 (cherkerboard)
    - Time-kill %85.7
- 18 olgu Karbapenem dirençli K.pneumoniae infeksiyonları(pnömoni, kan dolaşımı infeksiyonu, intraabdominal infeksiyon)
  - Ertapenem (1x1 gr) + meropenem (3x2 gr) (veya doripenem (3x500 mg))
  - Klinik başarı 7/18 (%39)
  - Mikrobiyolojik başarı 11/14 (%79)
  - Mortalite 5/18 (%28)

Olivia A et al. Clin Microbiol Infect 2016; 22:147-53.
Cprek JB et al. Antimicrob Agents Chemother 2015; 60:669-73.

De Pascale et al. Critical Care (2017) 21:173
DOI 10.1186/s13054-017-1769-z

Critical Care

RESEARCH Open Access

# Double carbapenem as a rescue strategy for the treatment of severe carbapenemase-producing *Klebsiella pneumoniae* infections: a two-center, matched case–control study

Gennaro De Pascale[1,6*], Gennaro Martucci[2], Luca Montini[1], Giovanna Panarello[2], Salvatore Lucio Cutuli[1], Daniele Di Carlo[3], Valentina Di Gravio[1], Roberta Di Stefano[4], Guido Capitanio[2], Maria Sole Vallecoccia[1], Piera Polidori[4], Teresa Spanu[5], Antonio Arcadipane[2] and Massimo Antonelli[1]

- Olgu kontrol (1:2)
- 48/96 olgu karbapenem dirençli *K.pneumoniae*
  - Kan dolaşımı infeksiyonu, yumuşak doku infeksiyonu, üriner sistem infeksiyonu
  - Çift Karbapenem – standart tedavi
  - Primer sonlanım: 28 günde mortalite
  - Sekonder sonlanım: Klinik kür, mikrobiyolojik erdikasyon, vazopressör ve MV süresi, 90 günde mortalite

**Table 2** Therapeutic and microbiological details according to the type of treatment

| Variable | Number (%) of patients | | *p* value |
|---|---|---|---|
| | DC group (*n* = 48) | ST group (*n* = 96) | |
| Polymicrobial infection | 6 (12.5) | 17 (17.7) | 0.57 |
| CR *Acinetobacter baumannii* | 3 (6.25) | 12 (12.5) | 0.4 |
| CR *Pseudomonas aeruginosa* | 3 (6.25) | 5 (5.2) | 0.89 |
| Combined targeted therapy | 35 (72.9) | 52 (54.2) | **0.05** |
| DC + colistin | 19 (39.6) | – | – |
| DC + gentamicin | 8 (16.9) | – | – |
| DC + tigecycline | 3 (6.25) | – | – |
| DC + colistin + tigecycline | 2 (4.2) | – | – |
| DC + colistin + gentamicin | 3 (6.25) | – | – |
| Colistin + tigecycline | – | 22 (22.9) | – |
| Colistin + gentamicin | – | 13 (13.5) | – |
| Gentamicin + tigecycline | – | 10 (10.4) | – |
| Colistin + tigecycline + gentamicin | – | 7 (7.3) | – |
| Extensively drug-resistant strains[a] | 32 (66.7) | 31 (32.3) | **<0.01** |
| Colistin MIC ≤ 2 μg/ml | 28 (58.3) | 64 (66.7) | 0.42 |
| Gentamicin MIC ≤ 2 μg/ml | 15 (31.3) | 72 (75) | **<0.01** |
| Tigecycline MIC ≤ 1 μg/ml[b] | 16 (47.1) | 58 (60.4) | 0.27 |
| Suboptimal MIC values[c] | 10 (20.8) | 14 (14.6) | 0.5 |

Bold data are significant

*DC* double carbapenem, *ST* standard treatment, *CR* carbapenem resistant, *MIC* minimal inhibitory concentration

[a]Strains resistant to at least one agent in all but two or fewer usually active antimicrobial categories

[b]MIC values were available in 130 patients: 34 pts (DC group) and 96 patients (ST group)

[c]Gentamicin (4 μg/ml), tigecycline (2 μg/ml)

De Pascale et al. Critical Care (2017) 21:173
DOI 10.1186/s13054-017-1769-z



RESEARCH Open Access

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| Değişken | ÇK grubu (n=48) (%) | Standart tedavi grubu (n=96) (%9 | *p* |
|---|---|---|---|
| **28 günlük mortalite** | **14 (29.2)** | **46 (47.9)** | **0.04** |
| 90 günlük mortalite | 24 (50) | 58 (60.4) | 0.31 |
| Klinik kür | 30 (62.5) | 47 (48.9) | 0.17 |
| Mikrobiyolojik eradikasyon | 22 (50) | 31 (38.3) | 0.27 |
| İnfeksiyon sonrası MV süresi | 14 (7.5-31) | 11.5 (7-19) | 0.16 |
| İnfeksiyon sonrası vazopressör süresi | 10.5 (3.5-27.5) | 8 (4.5-12) | 0.19 |

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- 28 gün mortalite ile ilgili Çok değişkenli lojistik regresyon analizi

| Değişken | p | Odds |
|---|---|---|
| SAPS II skoru | <0.01 | 1.08 |
| SOFA SKORU | ≤0.01 | 1.36 |
| Çift Karbapenem tedavisi | 0.002 | 0.33 |

**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<br>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. |

(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.

Bassetti M. et al. Curr Opin Infect Dis 2016; 29:583-94.

| 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. |

(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).
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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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| 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.
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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.

Bassetti M. et al. Curr Opin Infect Dis 2016; 29:583-94.

| İlaç | Genel/standart doz | KDE için doz önerisi ve yorum |
|---|---|---|
| Meropenem | 1gr/8 saat | Uzamış infüzyon 2 gr/8 saat (MİK 2-8 mg/L ise. Daha yüksek MİK değerlerinde etkili olmayabilir) |
| Ertapenem | 1gr/24 saat | Çift karbapenem rejimlerinde 2 gr/gün düşün |
| Kolistin | EMA: 6-9 MU yükleme sonrası 2-3 doza bölünmüş halde 9 MU/gün<br>FDA: 2.5-5 mg/kg/gün KBA | EMA dozu ağır KDE infeksiyonlarında önerilmekte.Yükleme dozu ve devamında yüksek doz ağır infeksiyon/şok tablosunda olmayanlarda tartışmalı |
| Polimiksin B | FDA: 1.5-2.5 mg/kg/gün (ikiye bölünmüş) | Hafif infeksiyonlarda ve izolatın MİK ≤1mg/L ise FDA dozu olasılıkla uygun; ağır infeksiyonlarda ve izolatın MİK >4mg/L ise 2-2.5 mg/kg yükleme dozu ardından ikiye bölünmüş olarak 3 mg/kg/gün önerilmektedir (tartışmalı) |
| Tigesiklin | 100 mg yükleme dozu ardından 50 mg/12 saat | HKP, kUSİ, KDİ veya şok tablolarında 200 mg yükleme dozu sonrası 100 mg/12 saat olarak vermeyi düşün |

Rodriguez-Bano J et al. Clin Microbiol Rev 2018; 31(2)

| İlaç | Genel/standart doz | KDE için doz önerisi ve yorum |
|---|---|---|
| Gentamisin, Tobramisin | 5-7 mg/kg/gün | HKP veya diğer seçeneklerin olmadığı şok durumlarında yüksek dozlar (10-15 mg/kg) düşünülebilir, ancak toksisite riski yüksektir, terapötik doz takibi önerilir |
| Amikasin | 15-20 mg/kg/gün | HKP veya diğer seçeneklerin olmadığı şok durumlarında yüksek dozlar (25-30 mg/kg) düşünülebilir, ancak toksisite riski yüksektir, terapötik doz takibi önerilir |
| Fosfomisin | 4 gr/6 saat – 8 gr/8 saat | Kombinasyonda kullan; yüksek sodyum yükü |
| Temosilin | 2 gr/8-12 saat | KPC (+) nadiren duyarlıdır; devamlı infüzyon ile FK/FD düzelir |
| Aztreonam | 1-2 gr/8 saat | MBL üretenler duyarlıdır |
| Seftazidim | 1-2 gr/8 saat | OXA-48 üretenler duyarlıdır |
| Seftazidim-avibaktam | 2.5 gr/8 saat | KPC (+) ve OXA-48 (+) sıklıkla duyarlıdır |
| Meropenem-vaborbaktam | 2/2 gr / 8 saat | KPC (+) sıklıkla duyarlıdır |

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| KDE infeksiyonu risk düzeyi, tedavi tipi, duyarlılık | İlaçlar |
|---|---|
| **Yüksek risk,** kombinasyon tedavisi β-laktam duyarlı (duyarlılık sonucuna göre) | *Omurga:* **Seftazidim-avibaktam** (tercih) veya **Meropenem-vaborbaktam**<br>Alternatif: **Meropenem** (MİK ≤8 mg/L ise) veya **Seftazidim** veya **Aztreonam**<br>*Ek ilaç:* Omurga olarak seftazimi/avibaktam veya meropenem/vaborbaktam kullanıldıysa: Kolistin, Tigesiklin, Aminoglikozid veya fosfomisin (eğer omurga ilaçları orta duyarlı ise bunlardan ikisini düşün) |
| Tüm β-laktam antibiyotiklere dirençli (meropenem MİK >8 mg/L), kolistin dahil en az 2 ilaca duyarlı | *Omurga:* **Kolistin**<br>*Ek ilaç:* Tigesiklin, aminoglikozid (nefrotoksisite riski yüksek) veya fosfomisin |
| Tüm β-laktam antibiyotiklere ve kolistine dirençli, en az 2 ilaca duyarlı | *Omurga:* **Tigesiklin** veya **aminoglikozid**<br>*Ek ilaç:* Tigesiklin veya aminoglikozid veya fosfomisin |
| PDR veya sadece 1 ilaca duyarlı<br><br>*Rodriguez-Bano J et al.* | **Meropenem + ertapenem** veya **Seftazidim-avibaktam + aztreonam**; buna Ek olarak duyarlılık sonucu veya sinerji testlerine göre bir antibiyotik |

| KDE infeksiyonu risk düzeyi, tedavi tipi, duyarlılık | İlaçlar |
|---|---|
| **Düşük risk,** monoterapi<br>Duyarlılık sonucuna göre | Seftazidim-avibaktam,<br>Meropenem-vaborbatam,<br>Meropenem<br>Seftazidim<br>Aztreonam<br>Kolistin<br>Tigesiklin<br>Aminoglikozid |

Yüksek Risk: septik şok veya kan dolaşımı infeksiyonu, INCREMENT skoru ≥8
Düşük Risk: INCREMENT skoru <8

*Rodriguez-Bano J et al. Clin Microbiol Rev 2018; 31(2)*

# INCREM

- Ağır sepsis ve s
- Pitt bakteriyemi
- Charlson index
- Kaynak kan dolaşımı
- Uygunsuz empirik tedavi

14 günlük mortalite

- 0-8 puan %18
- 9-13 %50
- 14-17 %80

*Tablo I.* Charlson Komorbidite İndeksi

| Komorbidite | Ağırlıklı puan* |
|---|---|
| Miyokard infarktüsü; konjestif kalp yetmezliği; periferal vasküler hastalık; serebrovasküler hastalık; demans; kronik akciğer hastalığı; konnektif doku hastalığı; ülser; hafif karaciğer hastalığı; diabetes mellitus | 1 |
| Hemipleji; orta/ağır böbrek yetmezliği; diyabet (hedef organ hasarı +); neoplazi; lösemi/lenfoma | 2 |
| Orta veya ağır karaciğer hastalığı | 3 |
| Metastatik solid tümör; AIDS | 6 |

* Toplam puan her bir komorbid durumun birbirine eklenmesiyle elde edilir. Kırk yaş üzerindeki her 10 yıl için bi puan eklenir (50-59: 1 puan, 60-69: 2 puan gibi).

*Table 1.* **The Pitt Bacteremia Score***

| Criterion | Points |
|---|---|
| Fever (oral temperature) | |
| ≤35°C or ≥40°C | 2 |
| 35.1–36.0°C or 39.0–39.9°C | 1 |
| 36.1–38.9°C | 0 |
| Hypotension<br>Acute hypotensive event with drop in systolic blood pressure > 30 mm Hg and diastolic blood pressure > 20 mm Hg<br>or<br>Requirement for intravenous vasopressor agents<br>or<br>Systolic blood pressure < 90 mm Hg | 2 |
| Mechanical ventilation | 2 |
| Cardiac arrest | 4 |
| Mental status | |
| Alert | 0 |
| Disoriented | 1 |
| Stuporous | 2 |
| Comatose | 4 |

* All criteria are graded within 48 hours before or on the day of first positive blood culture. The highest point score during that time is recorded.

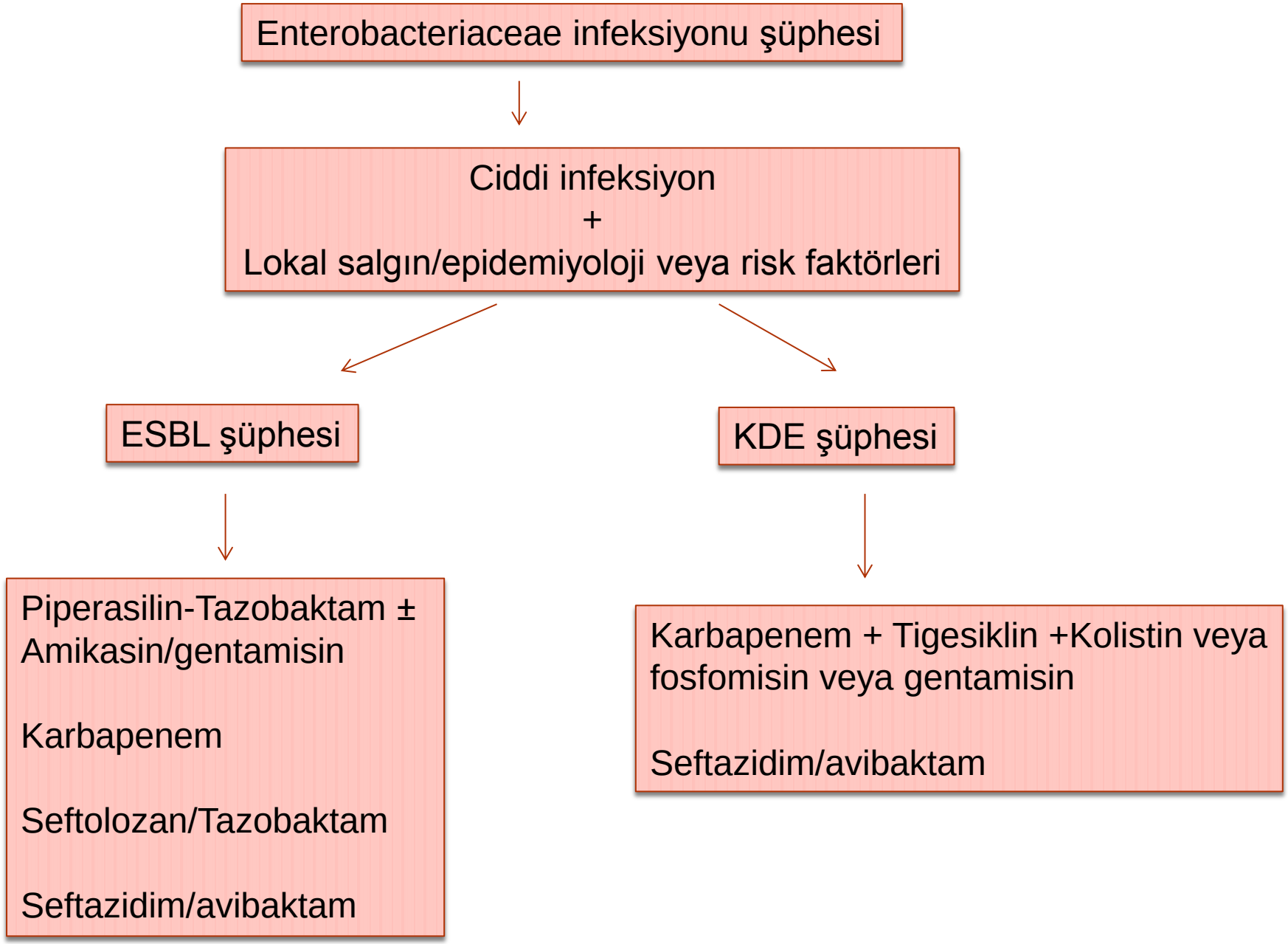
# ESBL, Karbapenem Dirençli Enterobacteriaceae Risk Faktörleri

Toplum kökenli
ESBL Risk Faktörleri
Yaş >70
DM
Charlson indeksi >3
Hastaneye başvuru öyküsü
Sağlık bakım merkezinden transfer
Üriner kateter kullanımı
Tekrarlayan veya obstruktif ÜSİ
Aminnopenilisin kullanımı
Sefalosporin kullanımı
Florokinolon kullanımı
Yüksek endemik yerden seyahat

Hastane kökenli
ESBL Risk Faktörleri
Lokal prevalans, salgın
Uzun süre hastanede yatma
İnvaziv girişimler
ESBL kolonizasyonu
Sefalosporin kullanımı
Florokinolon kullanımı
Karbapenem kullanımı

Hastane kökenli
KDE Risk Faktörleri
Lokal prevalans, salgın
Yaş >70
DM
Charlson indeksi >3
YBÜ
İnvaziv girişimler
Sefalosporin kullanımı
Florokinolon kullanımı
Karbapenem kullanımı

Bassetti M et al. Curr Opin Infect Dis 2016;29:583-94.




Bassetti M et al. Curr Opin Infect Dis 2016;29:583-94.

# Seftazidim-avibaktam

- Enterobacteriaceae, *P.aeruginosa*
- *Acinetobacter* spp., *S.maltophilia* MİK değerleri yüksek, yetersiz veri
- 4:1 (2 gr – 0.5 gr)
- Avibaktam: β-laktam olmayan β-laktamaz inhibitörü
- Tek başına etkisiz
- Seftazidimi serin β-laktamazlarına karşı korur

Shirley M. Drugs 2018;78:675-92.

# Seftazidim-avibaktam

- Avibaktam:
  - Ambler Sınıf A (TEM-1, CTX-M-15, KPC-2, KPC-3)
  - Ambler Sınıf C (AmpC)
  - Ambler Sınıf D (OXA-10, OXA-48) etkili

  - Ambler Sınıf B (NDM-1, IMP-1, metallobetalaktamazlar) etkisiz

Shirley M. Drugs 2018;78:675-92.

# Seftazidim-avibaktam

- 2015 Şubat ayında FDA onayı
- Komplike üriner sistem infeksiyonları/akut piyelonefrit
- Komplike intraabdominal infeksiyonlar
- Nozokomiyal pnömoni
- Ventilatör ilişkili pnömoni
- 3 x 2.5 gr i.v (100 mL sıvı içinde 2 saat infüzyon)

Shirley M. Drugs 2018;78:675-92.

# Fosfomisin

- Fosfonik asit
- Fosfomisin trometamol (oral)
- Fosfomisin disodyum (i.v)
- Hücre duvarı sentezinin erken evresinde etkili
- Geniş spektrumlu (*S.aureus* , *Enterococcus* spp., *S.pneumoniae*, Enterobacteriaceae, *P.aeruginosa* vs)
- Acinetobacter suşlarına karşı kolistin ile sinerjik, sulbaktam ile sinerjik
- KDE izolatlarında duyarlılığı değişken
- NDM-1 KDE duyarlılığı %94
- 12-24 gr/ gün
- Diyare, hipokalemi, sodyum yüklenmesi

Thaden et al. Virulence 2017;8(4):403-16.

TABLE 3 Synergistic activity of fosfomycin in combination with other antibiotics against several clinically relevant bacteria

| Organism(s) | Antibiotics with activity in combination with fosfomycin (reference[s]) | | |
|---|---|---|---|
| | Synergy | Indifference | Antagonism |
| *E. coli* | Gentamicin (137)[a] | | |
| ESBL-producing *E. coli* | Carbapenems (84),[a] aztreonam (153),colistin (84),[b] aminoglycosides (28, 84),[a] tigecycline (28, 84),[a] colistin (28) | | |
| ESBL-producing *K. pneumoniae* | Carbapenems (84), colistin (84),[b] netilmicin (84),[a] tigecycline (84)[a] | | |
| *K. pneumoniae* | Gentamicin (137)[a] | | |
| MDR *K. pneumoniae* | Carbapenem (152), aztreonam (153) | | |
| CR *K. pneumoniae* | Carbapenems (84, 164, 179), colistin (84, 164, 179),[a] tigecycline (84),[a] netilmicin (84)[a] | Gentamicin (179) | Colistin (156), (OXA-48-producing strain) |
| NDM-1-producing *Enterobacteriaceae* | | Colistin (158), tigecycline (158) | |
| *Salmonella* | Amilacin (137),[a] cefepime (137) | | |
| *P. aeruginosa* | Aztreonam (137),[a] levofloxacin (137),[a] ciprofloxacin (137),[a] cefepime (137),[a] gentamicin (137),[a] piperacillin (137),[a] ceftazidime (137),[a] imipenem (137)[a] | Imipenem (137), ceftazidime (137), ciprofloxacin (137), gentamicin (137) | |
| CR *P. aeruginosa* | Colistin (149),[a] carbapenems (149, 150),[a] aminoglycosides (27, 40), piperacillin-tazobactam (40), ceftazidime (40), cefepime (40), ciprofloxacin (40) | | |
| MDR *P. aeruginosa* | Carbapenems (84), colistin (189),[b] tigecycline (84),[b] netilmicin (84)[b] | Carbapenems (152), aminoglycosides (168) | |
| *Acinetobacter* | Amikacin (137)[a] | Imipenem (137), ceftazidime (137), ciprofloxacin (137) | |
| OXA-23-producing *Acinetobacter* | Colistin (59, 89),[a,b] sulbactam (89) | | |
| Pan-drug-resistant *Acinetobacter* | Polymyxin B (90),[b] minocycline (90)[b] | | |

# Plazomisin

- Aminoglikozid
- AG modifiye eden enzimlerden etkilenmemekte
  - KDE suşlarında Gentamisin, tobramisin, amikasine oranla daha etkili
- 16S rRNA metiltransferaz
- Faz III randomize çalışma (kÜSİ)
  - Plazomisin 15 mg/kg/gün
  - Meropenem 3x1 gr
- Faz III randomize çalışma (KDİ, nozokomiyal pnömoni/VİP)
  - Plazomisin ve kolistin, Tigesiklin veya meropenem ile kombine
  - Mortalite oranları %11.8-%40)
  - Renal toksisite daha az

# Eravasiklin

- Sentetik florosiklin
- Gram negatif türlere etkili
- KDE'a karşı tigesiklinden 2-4 kat daha etkin
- Komplike intraabdominal infeksiyonlar
  - Ertapenem-Eravasiklin (1.5 mg/kg/gün) karşılaştırılmış

# İmipenem-Relebaktam

- Relebaktam avibaktama benzer şekilde non-β -laktam serin β-laktamaz inhibitörü
- Enterobacteriaceae, *P.aeruginosa* suşlarında imipenem etkinliği artıyor
- Ancak *Acinetobacter baumannii* ve *S.maltophilia* suşlarında imipenem etkinliği değişmemekte

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**Table 4** In vitro activity (MIC, mg/L) of imipenem and imipenem–relebactam against Gram-negative aerobes

| Gram-negative aerobes | Imipenem | | | Imipenem–relebactam[a] | | | MIC fold reduction[c] |
|---|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$[b] | Range | $MIC_{50}$ | $MIC_{90}$[b] | Range | |
| *Acinetobacter baumannii* | 4 | >32 | ≤0.03 to >32 | 2 | >32 | ≤0.03 to >32 | – |
| Imipenem non-susceptible[d] | 32 | >32 | 4 to >32 | 32 | >32 | 4 to >32 | – |
| *Chryseobacteria* | 64[e] | NA | 32 to >64 | 32[e] | NA | 32–64 | 2 |
| *Enterobacter cloacae* | NA | NA | 4 to 8 | ≤0.25 | NA | ≤0.25 to ≤0.25 | NA |
| *Enterobacter* spp. | ≤0.5 | 1 | ≤0.03 to 32 | 0.25 | 0.5 | ≤0.03 to 2 | 2 |
| Imipenem non-susceptible[f] | NA | NA | 2–32 | NA | NA | 0.12–1 | NA |
| *Escherichia coli* | 0.25 | 0.25 | ≤0.03 to >30 | 0.25 | 0.25 | ≤0.03 to 1 | – |
| *Klebsiella pneumoniae* | ≤0.5 | ≤0.5 | ≤0.5 to >32 | 0.25 | 0.25 | ≤0.03 to 4 | – |
| Imipenem non-susceptible[f] | 8 | 32 | 4 to >32 | 0.25 | 2 | 0.06–4 | 16 |
| KPC producers | 16 | >16 | 0.5 to >16 | 0.25 | 1 | 0.12–2 | >16 |
| ESBL producers | 0.25 | 0.5 | 0.25–1 | 0.12 | 0.25 | 0.12–0.5 | 2 |
| *Pseudomonas aeruginosa* | 1 | 16 | ≤0.03 to >32 | 0.5 | 2 | ≤0.03 to >32 | 8 |
| Imipenem non-susceptible[d] | 16 | 32 | 4 to >32 | 2 | 4 | 0.25 to >32 | 8 |
| KPC producers | ≥8 | ≥8 | ≥8 to ≥8 | ≥8 | ≥8 | 1 to ≥8 | – |
| ESBL producers | ≥8 | ≥8 | ≥8 to ≥8 | 4 | ≥8 | 1 to ≥8 | – |
| Imipenem susceptible[g] | 1[e] | NA | 0.25–2 | 0.5[e] | NA | 0.12–0.5 | 2 |
| MDR[h], non-CF | 32[e] | NA | 8–64 | 4[e] | NA | 2–8 | 8 |
| MDR[h], CF | 64[e] | NA | 64 | 16[e] | NA | 8–16 | 4 |
| *Serratia marcescens* | NA | NA | 4 to >16 | NA | NA | ≤0.25 to 4 | NA |
| *Stenotrophomonas maltophilia* | >64 | >64 | 2 to >64 | >64 | >64 | 2 to >64 | – |
| Serine carbapenemase producers | 8 | >16 | 2 to >16 | ≤0.25 | 1 | ≤0.25 to 4 | >16 |
| Enterobacteriaceae, non-Proteeae[i] | ≤0.5 | 1 | ≤0.5 to >32 | 0.12 | 0.5 | ≤0.03 to >32 | 2 |
| Imipenem non-susceptible[f] | 2 | >32 | 2 to >32 | 1 | 2 | ≤0.5 to >32 | >16 |
| ESBL producers | 2[e] | NA | 2 to ≥8 | 0.5[e] | NA | ≤0.25 to 4 | 8 |
| KPC producers | 8 | 64 | 0.5 to >128 | 0.25 | 0.5 | 0.06–2 | 128 |

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# Meropenem-Vaborbaktam

- Vaborbaktam non-β-laktam, siklik, boronik asit bazlı β-laktamaz inhibitörü
- Enterobacteriaceae türlerinde meropenem ekinliği artıyor.
- *A.baumannii*, *S.maltophilia*, *P.aeruginosa*'da düzelmiyor

**Table 3** Activities of β-lactamase inhibitors against various β-lactamase enzymes

| | β-lactamase inhibitor | | | | | |
|---|---|---|---|---|---|---|
| | Relebactam | Vaborbactam | Avibactam | Clavulanic acid | Sulbactam | Tazobactam |
| Class A | | | | | | |
| TEM | + | + | + | + | + | + |
| SHV | + | + | + | + | + | + |
| CTX-M | + | + | + | + | + | + |
| KPC | + | + | + | − | − | − |
| Class B | | | | | | |
| MBL | − | − | − | − | − | − |
| Class C | | | | | | |
| AmpC | + | + | + | − | ±[a] | − |
| Class D | | | | | | |
| OXA | ± | −[b] | ± | − | − | − |
| Reference | [5] | [5] | [5, 24] | [25, 26] | [27] | [27] |

− no inhibitory activity, + inhibitory activity, *MBL* metallo-β-lactamase

[a]Enterobacteriaceae resist inhibition by sulbactam, although *Klebsiella* spp., *Salmonella* spp., and *Proteus* spp. normally do not harbor chromosomal $bla_{AmpC}$ genes

[b]Limited data available

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Table 7 In vitro activity (MIC, mg/L) of meropenem and meropenem–vaborbactam against Gram-negative aerobes

| Gram-negative aerobes | Meropenem | | | Meropenem–vaborbactam[a] | | | MIC fo reductic |
|---|---|---|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$[b] | Range | $MIC_{50}$ | $MIC_{90}$[b] | Range | |
| *Acinetobacter baumannii* | 32 | 64 | 4 to > 64 | 32 | 64 | 1 to > 64 | – |
| *Acinetobacter* spp. | NA | NA | NA | 32 | > 32 | 0.03 to > 32 | NA |
| *Citrobacter freundii* species complex | NA | NA | NA | ≤ 0.015 | 0.03 | ≤ 0.015 to 8 | NA |
| KPC producers | 4 | 8 | 1–8 | ≤ 0.06 | 0.12 | ≤ 0.06 to 0.25 | 64 |
| *Citrobacter* spp. | NA | NA | NA | ≤ 0.015 | 0.03 | ≤ 0.015 to 0.06 | NA |
| *Citrobacter koseri* | NA | NA | NA | ≤ 0.015 | 0.03 | ≤ 0.015 to 0.03 | NA |
| *Enterobacter aerogenes* | NA | NA | NA | 0.03 | 0.03 | ≤ 0.015 to 2 | NA |
| *Enterobacter cloacae* | 4 | 16 | ≤ 0.03 to > 64 | ≤ 0.06 | 0.25 | 0.03–4 | 64 |
| *Enterobacter cloacae* species complex | NA | NA | NA | ≤ 0.015 | 0.03 | ≤ 0.015 to 8 | NA |
| KPC producers | 8 | > 32 | 2 to > 32 | ≤ 0.03 | 0.12 | ≤ 0.03 to 0.12 | > 256 |
| *Escherichia coli* | ≤ 0.015 | 0.03 | ≤ 0.015 to > 32 | ≤ 0.015 | 0.03 | ≤ 0.015 to > 32 | – |
| Meropenem non-susceptible[d] | 4[e] | NA | 2 to 8 | ≤ 0.015[e] | NA | ≤ 0.015 to 0.5 | ≥ 256 |
| KPC producers | 4 | 8 | 0.5 to 32 | ≤ 0.03 | ≤ 0.03 | ≤ 0.03 to 0.12 | ≥ 256 |
| ESBL producers | ≤ 0.015 | 0.06 | ≤ 0.015 to 8 | ≤ 0.015 | 0.03 | ≤ 0.015 to 2 | 2 |
| *Klebsiella oxytoca* | NA | NA | NA | 0.03 | 0.03 | ≤ 0.015 to 16 | NA |
| KPC producers | 4 | 32 | 2 to > 64 | ≤ 0.06 | 0.5 | ≤ 0.06 to 2 | 64 |
| *Klebsiella pneumoniae* | 0.03 | 0.03 | ≤ 0.015 to > 32 | 0.03 | 0.03 | ≤ 0.015 to > 32 | – |
| Carbapenem non-susceptible[d] | 16 | > 32 | 2 to > 32 | 0.03 | 0.5 | ≤ 0.015 to > 32 | > 64 |
| KPC producers | 16 | 64 | 0.25 to > 64 | 0.03 | 1 | ≤ 0.004 to > 64 | 64 |
| ESBL producers | 0.03 | NA | ≤ 0.015 to 2 | 0.03 | 0.5 | ≤ 0.015 to 2 | – |
| *Klebsiella* spp., KPC producers | > 32 | > 32 | 2 to > 32 | 0.12 | 1 | ≤ 0.03 to > 32 | > 32 |
| *Proteus mirabilis* | NA | NA | NA | 0.06 | 0.12 | ≤ 0.015 to 16 | NA |
| *Proteus* spp., indole positive | NA | NA | NA | [illegible] | [illegible] | [illegible] | NA |
| *Pseudomonas aeruginosa* | 0.5 | 8 | ≤ 0.015 to > 64 | 0.5 | 8 | ≤ 0.015 to 64 | – |

Zhanel GG et al. Drugs. 2018; 78:65-98.

# En iyisi önlemek

- Standart el hijyeni
- Temas önlemlerinin alınması gereken kolonize-infekte olguların erken saptanması
- Aktif surveyans ve izolasyon
- Personel kohortu
- Antimikrobiyal yönetim
- Eğitim programları
- Çevresel yüzeylerin temizliği
- Klorheksidinli banyolar

# Gelecekte Neler Var?

- Antimikrobiyal peptidler
- Bakteriyofaj tedavileri
- Anti-virulans faktörler
- Fitokimyasallar
- LPS inhibitörleri
- Efflux pompa inhibitörleri

Bassetti M et al. Intensive Care Med 2017;43:1464-75.

# Özet

- MDR-XDR *A.baumannii* infeksiyonlarında
  - Kolistin monoterapisi ?
  - Kolistin kombinasyon tedavileri ?
  - Heterodirenç?
  - İnhaler tedaviler mikrobiyolojik eradikasyonda etkili
- PDR *A.baumannii* infeksiyonlarında
  - Kombinasyona devam
  - Hangi kombinasyon?
- Karbapenem dirençli *K.pneumoniae* infeksiyonlarında
  - Meropenem MİK düzeyi önemli
  - Kombinasyon
  - Seftazidim-avibaktam