

# Karbapeneme Dirençli Gram Negatif İnfeksiyonların Tedavisi: Neredeyiz?

## *Acinetobacter baumannii*

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Başkent Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

Klimik mobil / [uygulama.klimik.org.tr](http://uygulama.klimik.org.tr)

- Kateter ilişkili idrar yolu infeksiyonunda etken sadece kolistin duyarlı *A. baumannii* ise tedavide hangisini seçersiniz?
  1. Sadece kolistin
  2. Sadece polimiksin B
  3. Karbapenem ve polimiksin kombinasyonu
  4. Ampisilin-sulbaktam ve polimiksin kombinasyonu
  5. Tigesiklin ve polimiksin kombinasyonu
  6. Diğer

# Klimik mobil / [uygulama.klimik.org.tr](http://uygulama.klimik.org.tr)

- Ventilatör ilişkili pnömonide etken sadece kolistin duyarlı *A. baumannii* ise tedavide hangisini seçersiniz?
  1. Sadece kolistin
  2. Sadece polimiksin B
  3. Karbapenem ve polimiksin kombinasyonu
  4. Ampisilin-sulbaktam ve polimiksin kombinasyonu
  5. Tigesiklin ve polimiksin kombinasyonu
  6. Diğer

# Acinetobacter baumannii

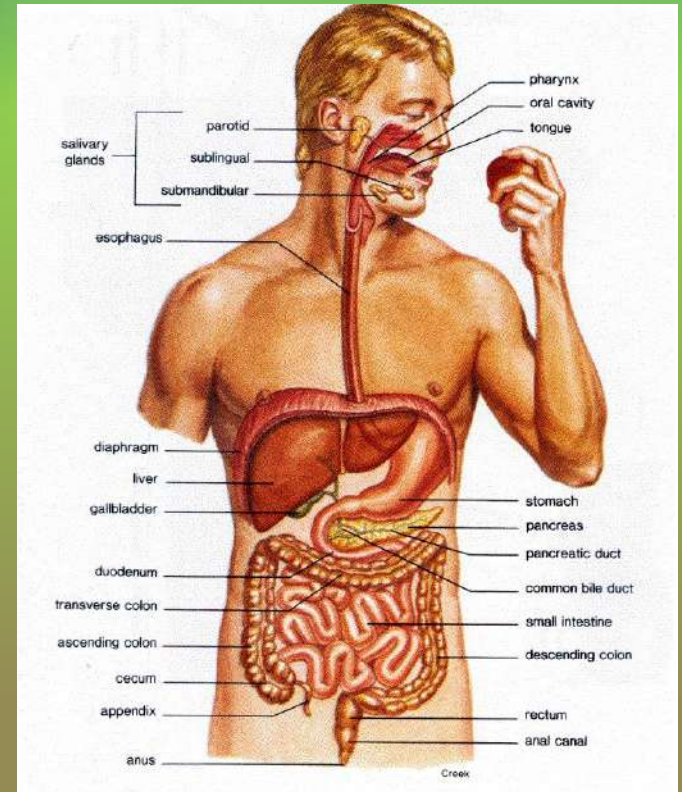


Gram negatif kokobasil  
Aerobik, hareketsiz  
Katalaz pozitif  
Oksidaz negatif  
Standart kùltùrlerde  
kolayca ùrer

Toprak, su, diğerk doğall ortamlarda yaygın

Sağlıklı bireylerde

- Cilt, konjunktiva
- Orofarenks/solunum yolları
- Gastrointestinal sistem
- Genitoüriner sistemde kolonize olabilir

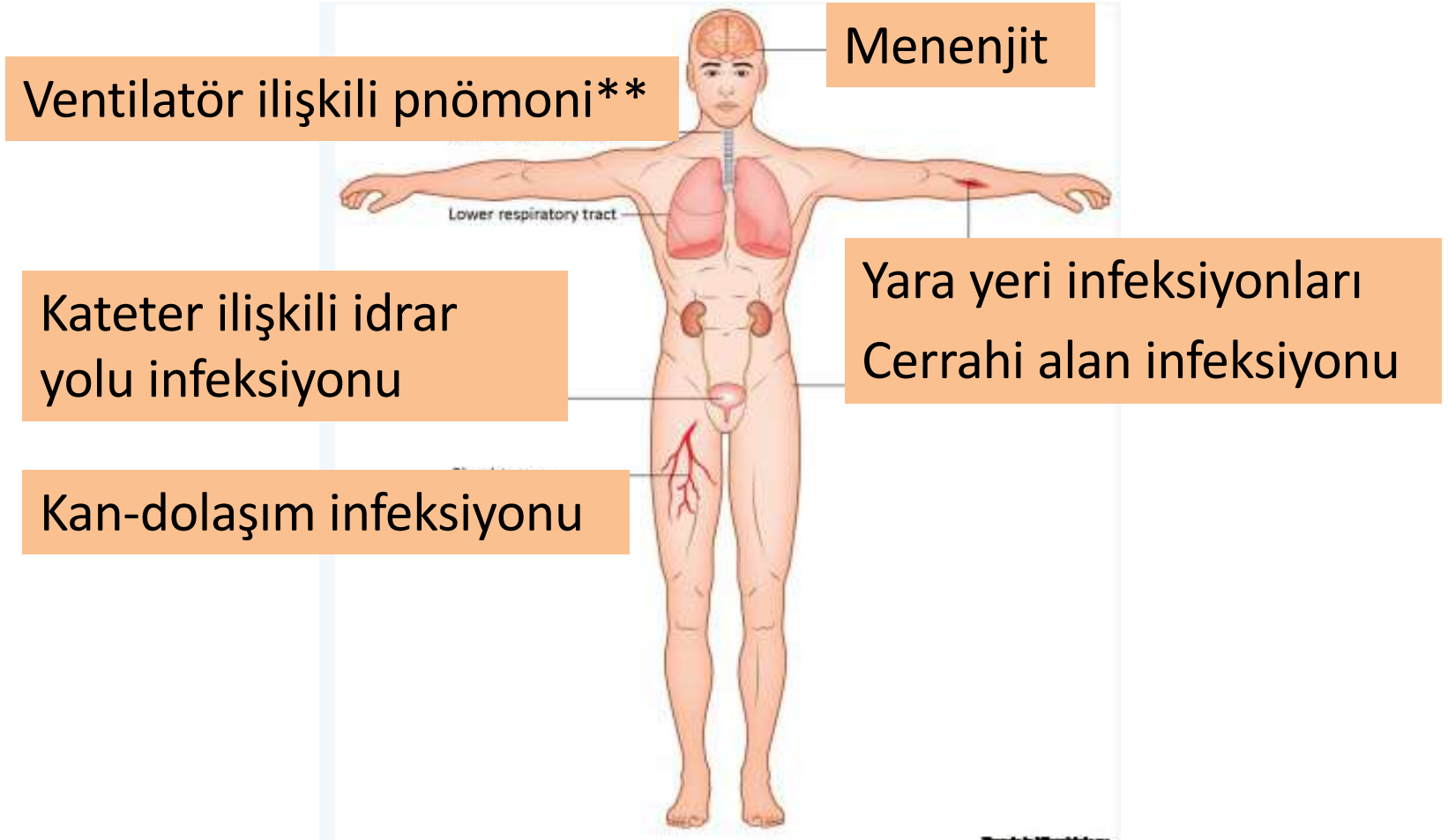




Hastanelerde...  
Bilirsiniz...  
Her yerden izole  
edilebilir



# Çeşitli enfeksiyonlara neden olur...



## Priority 1: CRITICAL<sup>#</sup>

*Acinetobacter baumannii*, carbapenem-resistant

*Pseudomonas aeruginosa*, carbapenem-resistant

*Enterobacteriaceae*<sup>\*</sup>, carbapenem-resistant, 3<sup>rd</sup> generation cephalosporin-resistant

Karbapenem dirençli  
*Acinetobacter baumannii*  
(KRAB)

## Priority 2: HIGH

*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*, 3<sup>rd</sup> generation cephalosporin-resistant, fluoroquinolone-resistant

2017'de DSÖ  
kritik öncelikli  
patojen ilan etti

## Priority 3: MEDIUM

*Streptococcus pneumoniae*, penicillin-non-susceptible

*Haemophilus influenzae*, ampicillin-resistant

*Shigella spp.*, fluoroquinolone-resistant

<sup>#</sup> *Mycobacteria* (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), was not subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.

<sup>\*</sup> Enterobacteriaceae include: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter spp.*, *Serratia spp.*, *Proteus spp.*, and *Providencia spp.*, *Morganella spp.*



# ABD raporu 2019

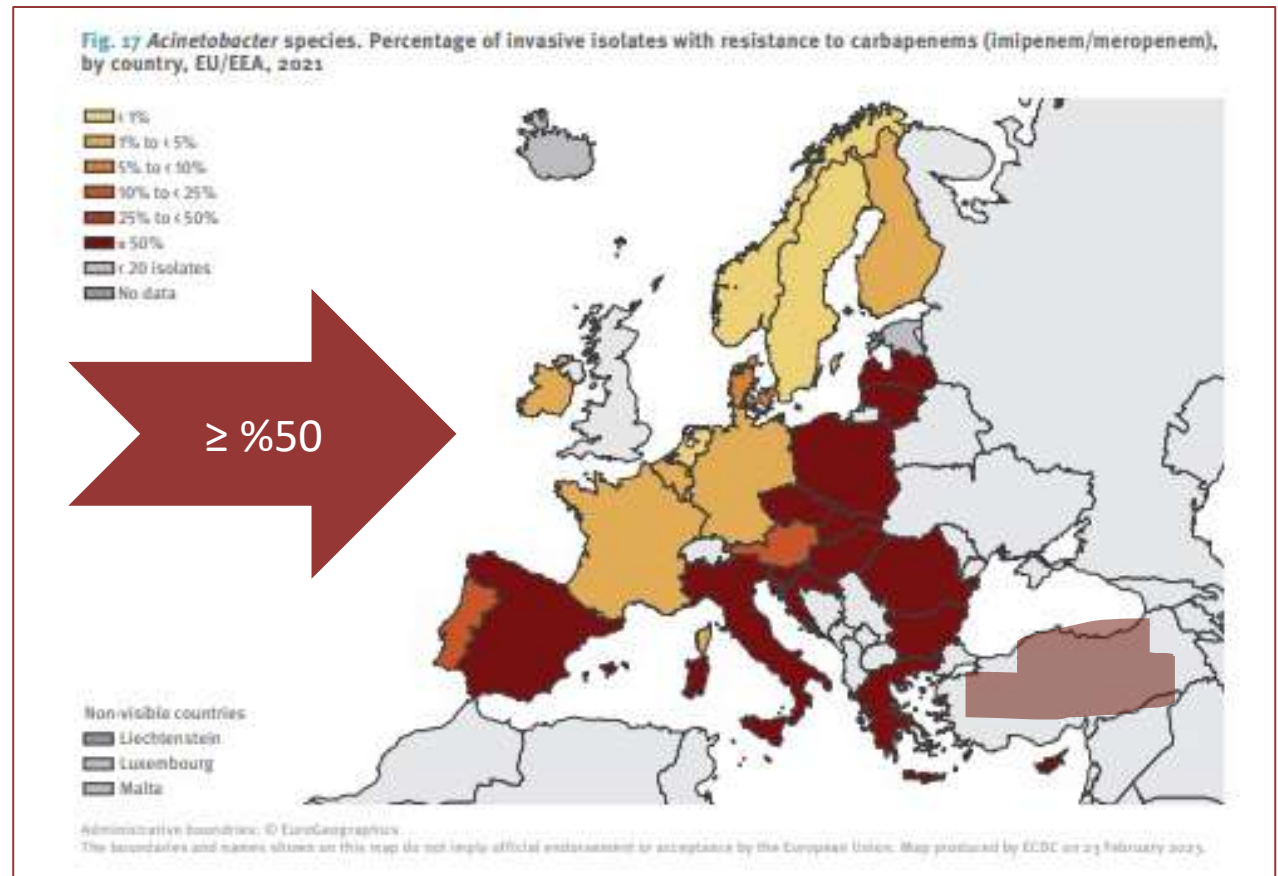


8500  
hastaneye  
yatış

700 ölüm

281milyon \$  
maliyet

# Avrupa'da karbapenem dirençli *A. baumannii*



# Ülkemizde durum

Total number of invasive isolates tested (n) and percentage of isolates with resistance phenotype (%)\*, by bacterial species and antimicrobial group/agent, Türkiye, 2017–2021

| Bacterial species  | Antimicrobial group/agent  | 2017 |      | 2018 |      | 2019 |      | 2020 |      | 2021 |      | Trend 2017–2021 |
|--|--|------|------|------|------|------|------|------|------|------|------|-----------------|
|  |  | n    | %    | n    | %    | n    | %    | n    | %    | n    | %    |                 |
| <i>E. coli</i>   | Aminoglycoside (gentamicin/kanamycin) resistance   | 3452 | 77.7 | 4194 | 76.7 | 4220 | 78.8 | 3562 | 76.1 | 4285 | 74.8 | ↔†              |
|  | Third-generation cephalosporin (ceftriaxone/cefotaxime)/cefazidime resistance                | 4137 | 92.7 | 4923 | 93.3 | 4847 | 94.7 | 4242 | 93.4 | 4852 | 94.2 | ↔†              |
|  | Carbapenem (meropenem/ertapenem) resistance  | 4121 | 92.7 | 4750 | 93.5 | 4965 | 93.9 | 4347 | 93.7 | 4551 | 87.9 | ↔†              |
|  | Fluoroquinolone (ciprofloxacin/levofloxacin) resistance                                      | 4022 | 89.3 | 4606 | 87.2 | 4855 | 91.7 | 4191 | 90.1 | 4707 | 90.9 | ↔               |
|  | Aminoglycoside (gentamicin/tobramycin) resistance  | 4083 | 90.6 | 4785 | 90.4 | 4437 | 84.8 | 4211 | 90.7 | 4560 | 86.6 | ↔               |
| Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides | 3755   | 83.8 | 4477 | 84.7 | 4694 | 88.3 | 4078 | 88.5 | 4395 | 83.9 | ↔    |                 |
| <i>K. pneumoniae</i>   | Third-generation cephalosporin (ceftriaxone/cefotaxime)/cefazidime resistance                | 3107 | 72.0 | 3765 | 72.0 | 3977 | 74.0 | 4101 | 74.9 | 4738 | 75.4 | ↔†              |
|  | Carbapenem (meropenem/ertapenem) resistance  | 3195 | 72.5 | 3440 | 66.4 | 4036 | 76.4 | 4187 | 74.7 | 4471 | 69.4 | ↔†              |
|  | Fluoroquinolone (ciprofloxacin/levofloxacin) resistance                                      | 2009 | 41.1 | 2357 | 42.6 | 2923 | 54.8 | 4275 | 69.0 | 4483 | 64.6 | ↔†              |
|  | Aminoglycoside (gentamicin/tobramycin) resistance  | 1993 | 44.4 | 2432 | 45.9 | 2925 | 54.8 | 4005 | 64.6 | 4482 | 61.2 | ↔               |
|  | Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides | 2421 | 55.9 | 2442 | 45.8 | 2689 | 49.5 | 4154 | 63.3 | 4203 | 59.7 | ↔               |
| <i>P. aeruginosa</i>   | Piperacillin-tazobactam resistance   | 1401 | 37.2 | 1464 | 36.0 | 1931 | 36.1 | 1361 | 33.1 | 1704 | 33.5 | ↔               |
|  | Cefazidime resistance  | 1481 | 38.0 | 1700 | 35.8 | 1645 | 28.0 | 1468 | 27.2 | 1723 | 28.3 | ↔               |
|  | Carbapenem (meropenem/ertapenem) resistance  | 1504 | 37.4 | 1682 | 35.5 | 1711 | 30.4 | 1541 | 30.2 | 1718 | 30.0 | ↔               |
|  | Fluoroquinolone (ciprofloxacin/levofloxacin) resistance                                      | 1223 | 25.6 | 1074 | 22.7 | 1037 | 19.2 | 1003 | 19.0 | 1725 | 33.3 | ↔               |
|  | Aminoglycoside (gentamicin/tobramycin) resistance  | 1114 | 26.7 | 1183 | 24.8 | 1481 | 26.8 | 1405 | 27.6 | 1660 | 27.8 | ↔†              |
| Combined resistance to aminoglycosides, carbapenems, fluoroquinolones and aminoglycosides†   | 1279   | 31.7 | 1401 | 27.8 | 1424 | 26.1 | 1172 | 22.5 | 1301 | 23.1 | ↔    |                 |
| <i>A. baumannii</i> spp.   | Carbapenem (meropenem/ertapenem) resistance  | 2540 | 93.6 | 2443 | 92.2 | 2390 | 90.4 | 3195 | 94.1 | 3229 | 91.8 | ↔               |
|  | Fluoroquinolone (ciprofloxacin/levofloxacin) resistance                                      | 2205 | 82.6 | 2297 | 84.4 | 2291 | 82.7 | 2664 | 78.0 | 2233 | 64.8 | ↔               |
|  | Aminoglycoside (gentamicin/tobramycin) resistance  | 2058 | 76.3 | 2104 | 78.1 | 2405 | 80.3 | 1117 | 32.1 | 1405 | 40.5 | ↔†              |
|  | Combined resistance to carbapenems, fluoroquinolones and aminoglycosides                     | 1421 | 52.0 | 1520 | 55.3 | 2062 | 75.6 | 2039 | 60.7 | 2089 | 60.8 | ↔†              |
| <i>S. aureus</i>   | MSSA <sup>b</sup>  | 1742 | 25.8 | 1716 | 25.4 | 1407 | 21.3 | 1391 | 21.4 | 1562 | 22.7 | ↔†              |
|  | MecA-mediated wild-type <sup>c</sup>   | 211  | 46.0 | 241  | 43.6 | 212  | 30.9 | 128  | 19.9 | 147  | 15.7 | ↔               |
| <i>S. pneumoniae</i>   | Macrolide (azithromycin/clarithromycin/erythromycin) resistance                              | 388  | 35.6 | 217  | 37.3 | 211  | 37.0 | 119  | 16.6 | 126  | 18.1 | ↔               |
|  | Combined penicillin non-wild-type and resistance to macrolides <sup>d</sup>                  | 184  | 29.0 | 211  | 34.0 | 214  | 31.5 | 117  | 27.4 | 123  | 24.0 | ↔               |
| <i>S. pneumoniae</i>   | High-level penicillin resistance   | 1125 | 38.0 | 1137 | 34.0 | 1014 | 31.5 | 2040 | 29.6 | 1809 | 24.7 | ↔†              |
|  | Vancomycin resistance  | 155  | 11.2 | 1579 | 15.6 | 1197 | 13.3 | 2201 | 15.4 | 2242 | 15.8 | ↔               |

\* Percentages of isolates with resistance phenotype are presented only if data are available for at least 10 isolates. If not, the percentage is presented as not applicable (NA).  
† † and ‡ indicate statistically significant increasing and decreasing trends, respectively, in the overall data. † indicates non-significance in the form of a significant trend in the data that only included laboratories reporting continuously for all five years; ‡ indicates no statistically significant trend. NA: not applicable indicates that the data were not reported for all years; a significant change in data source occurred during the period, or the number of isolates was  $\leq 10$  in any year during the period.  
<sup>a</sup> The percentage of MSSA isolates is not reported from 2020 onwards.



| Acinetobacter baumannii              | 2018 | 2019 | 2020 | 2021 |   |
|--------------------------------------|------|------|------|------|---|
| Karbapenem R                         | 92   | 90   | 93   | 93   | ↑ |
| Kinolon R                            | 94   | 90   | 93   | 94   |   |
| Aminoglikozid R                      | 79   | 80   | 86   | 85   |   |
| Karbapenem, kinolon, aminoglikozid R | 79   | 79   | 84   | 84   |   |

# Tedavide sorunlar

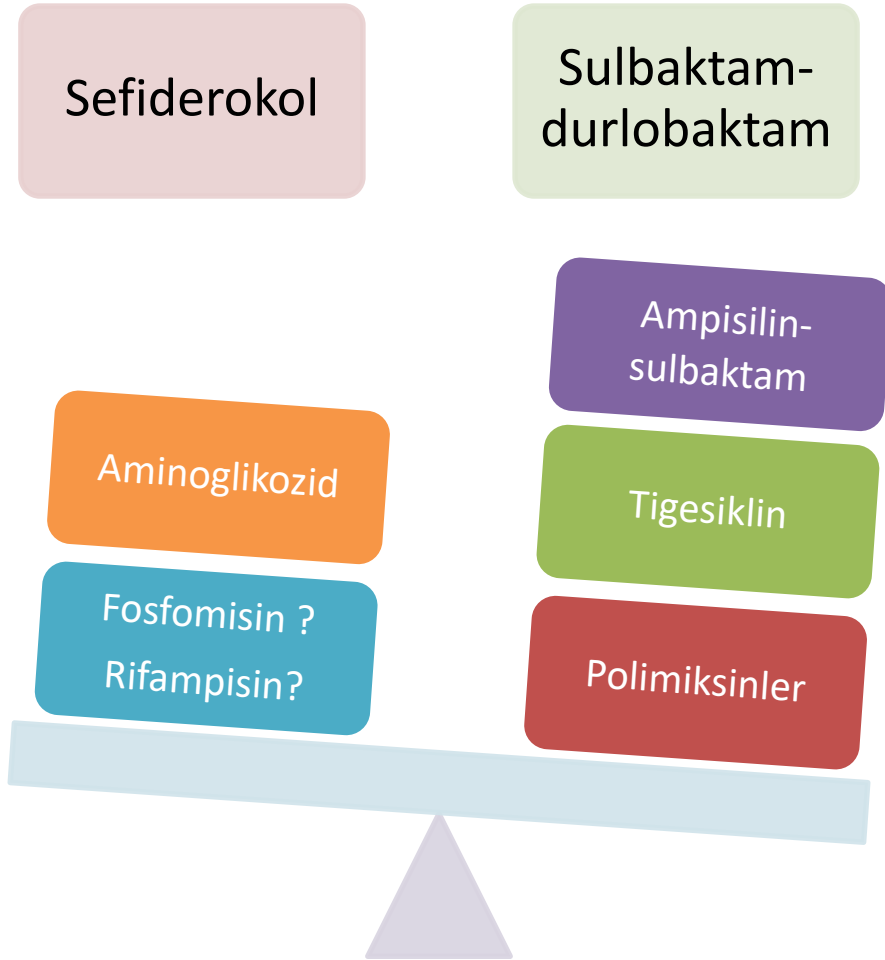
Kolonizasyon mu?  
Etken mi?

Antibiyotiklerin  
parlak çağı bitti,  
etkili antibiyotik yok

Standart tedavi?  
Monoterapi?  
Kombinasyon?

Çalışmalarda hasta  
sayısı kısıtlı, hasta ve  
kombinasyonlar  
çeşitli

# Tedavi seenekleri



# ESCMID kılavuzunda in vitro aktif tedavi seçenekleri

**Table 2**  
Potential *in vitro* activity of antibiotics against target carbapenem-resistant Gram-negative bacteria and approved ir

|                                | CRAB | ESBLs | CRPA non-MBL | CRE non-CP | CRE-KPC | CRE-OXA-48 | CRE-MBL |
|--------------------------------|------|-------|--------------|------------|---------|------------|---------|
| <b>New antibiotics</b>         |      |       |              |            |         |            |         |
| Ceftolozane-tazobactam         | No   | Yes   | Yes          | No         | No      | No         | No      |
| Ceftazidime-avibactam          | No   | Yes   | Yes          | +/-        | Yes     | Yes        | No      |
| Meropenem-vaborbactam          | No   | Yes   | No           | +/-        | Yes     | No         | No      |
| Imipenem-cilastatin/relebactam | No   | Yes   | Yes          | +/-        | Yes     | No         | No      |
| Plazomicin                     | No   | Yes   | +/-          | Yes        | Yes     | Yes        | +/-     |
| Eravacycline                   | Yes  | Yes   | No           | Yes        | Yes     | Yes        | Yes     |
| Cefiderocol                    | Yes  | Yes   | Yes          | Yes        | Yes     | Yes        | Yes     |
| <b>Old antibiotics</b>         |      |       |              |            |         |            |         |
| Polymyxins                     | Yes  | Yes   | Yes          | Yes        | Yes     | Yes        | Yes     |
| <b>Aminoglycosides</b>         |      |       |              |            |         |            |         |
| Aminoglycosides                | +/-  | +/-   | +/-          | +/-        | +/-     | +/-        | +/-     |
| Fosfomycin iv                  | No   | Yes   | +/-          | +/-        | +/-     | +/-        | +/-     |
| Aztreonam                      | No   | No    | +/-          | No         | No      | No         | +/-     |
| Tigecycline                    | Yes  | Yes   | No           | Yes        | Yes     | Yes        | Yes     |
| Temocillin                     | No   | Yes   | No           | No         | +/-     | No         | No      |

|                                 | KRAB |
|---------------------------------|------|
| <del>Seftazidim-avibaktam</del> | No   |
| Seftolozan-tazobaktam           | No   |
| Meropenem-vaborbaktam           | No   |
| İmipenem-relabaktam             | No   |
| Sefiderokol                     | Yes  |
| Tigesiklin/Eravasiklin          | Yes  |
| Polimiksin                      | Yes  |
| Aminoglikozid                   | +/-  |
| Fosfomisin                      | No   |



## Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Pranita D. Tamma,<sup>1,2</sup> Samuel L. Aitken,<sup>2</sup> Robert A. Bonomo,<sup>3</sup> Amy J. Mathers,<sup>4,5</sup> David van Duin,<sup>6</sup> and Cornelius J. Clancy<sup>7</sup>

<sup>1</sup>Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; <sup>2</sup>Department of Pharmacy, University of Michigan Health, Ann Arbor, Michigan, USA; <sup>3</sup>Medical Service and Center for Antimicrobial Resistance and Epidemiology, Louis Stokes Cleveland Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA; <sup>4</sup>Department of Medicine, University of Virginia, Charlottesville, Virginia, USA; <sup>5</sup>Department of Pathology, University of Virginia, Charlottesville, Virginia, USA; <sup>6</sup>Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA and <sup>7</sup>Department of Medicine, University of Pittsburgh Pittsburgh, Pennsylvania, USA

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KRAB tedavi genel öneri;  
Yüksek doz ampicilin-  
sulbaktam (6-9gr sulbaktam)  
+ önerilen bir ajan ile  
kombinasyon  
(polimiksin, tigesiklin,  
sefiderokol)



### Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul<sup>1,2,i</sup>, Elena Carrara<sup>3,i</sup>, Pilar Retamar<sup>4,5</sup>, Thomas Tängdén<sup>6</sup>, Roni Bitterman<sup>1,2</sup>, Robert A. Bonomo<sup>7,8,9</sup>, Jan de Waele<sup>10</sup>, George L. Daikos<sup>11</sup>, Murat Akova<sup>12</sup>, Stephan Harbarth<sup>13</sup>, Celine Pulcini<sup>14,15</sup>, José Garnacho-Montero<sup>16</sup>, Katja Seme<sup>17</sup>, Mario Tumbarello<sup>18</sup>, Paul Christoffer Lindemann<sup>19</sup>, Sumanth Gandra<sup>20</sup>, Yunsong Yu<sup>21,22,23</sup>, Matteo Bassetti<sup>24,25</sup>, Johan W. Mouton<sup>26,1</sup>

KRAB tedavi genel öneri;  
•Sulbaktam duyarlı VIP  
ampicilin-sulbaktam  
•Sulbaktam dirençli, in vitro  
aktif ise polimiksin veya  
yüksek doz tigesiklin  
•Sefiderokol (düşük kanıt)

# Sulbaktamın rolü

- Sulbaktam;
  - $\beta$ -laktamaz inhibitörü
    - Sadece Ambler klas A'ya etkin
    - Metallo  $\beta$ -laktamaza etkisiz
- KRAB izolatlarınınin >%50 ampisilin-sulbaktam dirençli
- Yine de
  - Sulbaktam'ın PBP etkisi nedeni ile
    - direnç durumuna bakılmaksızın etkin bir seçenek olabilir

## Ambler Classification of $\beta$ -lactamases

| Ambler Class  | A  | B   | C  | D   |
|---------------|--|---|--|---|
| Active Site   | Serine   | Metallo<br>(zinc-binding thiol)             | Serine   | Serine  |
| Enzyme Type   | TEM, SHV,<br>CTX-M, KPC  | NDM-1, IMP,<br>VIM                          | AmpC, CMY  | OXA   |
| Host Organism | Enterobacteriaceae<br>and<br>Non-fermenters  | Enterobacteriaceae<br>and<br>Non-fermenters | <i>Enterobacter</i> spp.<br><i>Citrobacter</i> spp.            | Enterobacteriaceae<br>and<br>Non-fermenters                         |
| Substrates    | Ampicillin; cephalotin;<br>penicillins; 3 <sup>rd</sup> gen<br>cephalosporins; Extended-<br>spectrum ce phalosporins;<br>carbapenems | All $\beta$ -lactams                        | Cephameycins;<br>3 <sup>rd</sup> -generation<br>cephalosporins | Cloxacillin;<br>Extended-spectrum<br>cephalosporins;<br>carbapenems |

# Literatürde Ampisilin-sulbaktam ve KRAB

Randomized Controlled Trial > Scand J Infect Dis. 2007;39(1):38-43.  
doi: 10.1080/00365540600951184.

**High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii***

Alex P. Betrosian<sup>1</sup>, Frantzeska Frantzeskaki, Anna Xanthaki, George Georgiadis

> Am J Ther. 2016 Jan-Feb;23(1):e78-85. doi: 10.1097/MIT.0b013e3182a32df3.

**Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Ventilator-Associated Pneumonia: Retrospective Comparison Between Intravenous Colistin and Intravenous Ampicillin-Sulbactam**

Ronen Zalts<sup>1</sup>, Ami Neuberger, Khetam Hussein, Ayelet Raz-Pasteur, Yuval Geffen, Tanya Mashliah, Renato Finkelstein

> Infez Med. 2019; Mar 1;27(1):11-16.

**Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii*: a case series study**

Stelios F. Assimakopoulos<sup>1</sup>, Vassilis Karamouzos<sup>2</sup>, Aikaterini Lefkaditi<sup>2</sup>, Christina Sklavou<sup>2</sup>, Fevronia Kolonitsiou<sup>3</sup>, Mirto Christofidou<sup>3</sup>, Fotini Filigou<sup>2</sup>, Charalambos Gogos<sup>1</sup>, Markos Marangos<sup>1</sup>

Research Article

**Colistin versus Colistin Combined with Ampicillin-Sulbactam for Multiresistant *Acinetobacter baumannii* Ventilator-associated Pneumonia Treatment: An Open-label Prospective Study**

Dimitrios Makris, Eli Paliakli<sup>1</sup>, Vasiliki Tsiali, Eleftherios Manolakis, Konstantinos Mertzakis, Olympia Apostolopoulou, Dimitris Spyridi, Epaminondas Zakynthinos

Departments of Critical Care and Microbiology, University Hospital of Larissa, Larissa, Intensive Care Unit, Larissa General Hospital, Larissa, Greece

%66 klinik iyileşme  
%77 mikrobiyolojik kür



Kolistinden iyi klinik ve mikrobiyolojik yanıt

VİP tedavisinde etkin

Kolistin ile kombinasyonda monoterapiye göre etkin sonuçlar

# Literatürde Ampisilin-sulbaktam ve KRAB

Jung et al. Critical Care (2017) 21:319  
DOI 10.1186/s13054-017-1916-6

Critical Care

RESEARCH

Open Access



Antimicrobials for the treatment of drug-resistant *Acinetobacter baumannii* pneumonia in critically ill patients: a systemic review and Bayesian network meta-analysis

Su Young Jung<sup>1,2</sup>, Seung Hee Lee<sup>1</sup>, Soo Young Lee<sup>3,4</sup>, Seungwon Yang<sup>5</sup>, Hayeon Noh<sup>5</sup>, Eun Kyoung Chung<sup>3,†</sup> and Jangik I. Lee<sup>1,2,\*†</sup>

Journal of Global Antimicrobial Resistance 24 (2021) 136–147

Contents lists available at ScienceDirect



Journal of Global Antimicrobial Resistance

journal homepage: [www.elsevier.com/locate/jgar](http://www.elsevier.com/locate/jgar)

Review

Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant *Acinetobacter baumannii* infections: A systematic review and network meta-analysis

Jiating Liu<sup>a,b</sup>, Yunfeng Shu<sup>a,b</sup>, Feilong Zhu<sup>c</sup>, Bimin Feng<sup>a</sup>, Zhengjie Zhang<sup>a,b</sup>, Liang Liu<sup>a,b</sup>, Guojun Wang<sup>b,\*</sup>

- 23 çalışma, 2118 hasta
- Meta-analiz
- A. baumannii pnömoni
- 15 farklı monoterapi ve kombinasyon karşılaştırılmış



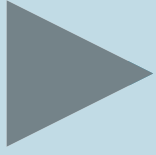
Sulbaktam mortalite üzerine diğerlerinden üstün

- 18 çalışma, 1835 hasta
- Yüksek doz sulbaktamli kombinasyonlar - kolistin bazli kombinasyonlar karşılaştırılmış

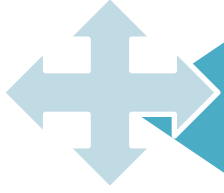


Klinik iyileşme, mortalite, nefrotoksik sulbaktamli rejimlerde daha iyi sonuç

# Polimiksinler ve A.baumannii



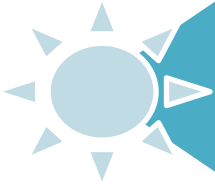
Polimiksinlerin KRAB'a karşı in vitro aktivitesi 



Polimiksinler, KRAB tedavisinde kombinasyon (IDSA, ESCMID)



Polimiksin B'nin farmakokinetik profili kolistinden iyi



Kolistin, idrarda aktif formuna dönüştüğü için KRAB üriner sistem infeksiyonlarında tercih nedeni

# Polimiksin monoterapisi neden önerilmiyor



Değişken serum polimiksin konsantrasyonları bakterisidal aktivite etkinliğini düşürür



Tedavi dozları nefrotoksisite eşiğine yakın



Akciğerlerde istenen konsantrasyona ulaşamamakta



Polimiksin monoterapisinde klinik başarısızlık ve direnç dair raporlar



# Tetrasiklin deriveleri ve A.baumannii



## Tetrasiklin deriveleri

- Minosiklin, tigesiklin, eravasiklin
- KRAB'a karşı in vitro etkili



## Minosiklin öncelikli öneri (IDSA)

- uzun süreli klinik deneyim
- CLSI duyarlılık yorumlama kriterlerinin varlığı



## Yüksek doz tigesiklin alternatif

Eravasiklin veri kısıtlılığı nedeni ile önerilmemekte

# Tetrasiklin deriveleri ve A.baumannii



## Tetrasiklin deriveleri

- Minosiklin, tigesiklin, eravasiklin
- KRAB'a karşı in vitro etkili

Tedavi de yüksek doz tigesiklin kombinasyon bileşeni olabilir  
(IDSA, ESCMID)

Yüksek doz tigesiklin= 200mg yükleme 2x100mg idame



## Yüksek doz tigesiklin alternatif

Eravasiklin veri kısıtlılığı nedeni ile önerilmemekte

# Tigesiklin vs. Sulbaktam

Eur J Clin Microbiol Infect Dis (2013) 32:1211–1220  
DOI 10.1007/s10096-013-1870-4

ARTICLE

**Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter baumannii* infections**

Y.-T. Lee · S.-M. Tsao · P.-R. Hsueh


RESEARCH ARTICLE

Open


Tigecycline-based versus sulbactam-based treatment for pneumonia involving multidrug-resistant *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex

Jung-Jr Ye<sup>1</sup>, Huang-Shen Lin<sup>2</sup>, Chun-Fu Yeh<sup>1</sup>, Yen-Mu Wu<sup>1</sup>, Po-Yen Huang<sup>1</sup>, Chien-Chang Yang<sup>1</sup>, Ching-Tai Huang<sup>1</sup> and Ming-Hsun Lee<sup>1\*</sup>

- 386 hasta
- İmipenem+sulbaktam
- Tigesiklin+  $\beta$ -laktam
- 30 günlük mortalite ve hastanede kalış süresinde fark yok

 Mikrobiyolojik yanıt tigesiklin kolunda **düşük**

- MDR-AB:  $\beta$ -laktam, kinolon, aminoglikozid dirençli
- 84 tigesiklin bazlı rejim
- 84 sulbaktam bazlı rejim
- Klinik yanıt ve mortalite de fark yok

 Mikrobiyolojik yanıt tigesiklin kolunda **düşük**

# Tigesiklin vs. Sulbaktam

Eur J Clin Microbiol Infect Dis (2013) 32:1211–1220  
DOI 10.1007/s10096-013-1870-4

ARTICLE

**Clinical outcomes of tigecycline alone or in combination with other antimicrobial agents for the treatment of patients with healthcare-associated multidrug-resistant *Acinetobacter***

Y.-T. Lee · S.-M.

RESEARCH ARTICLE

Open

Tigecycline-based versus sulbactam-based treatment for pneumonia involving multidrug-resistant *Acinetobacter calcoaceticus*-*Acinetobacter baumannii* complex

ang<sup>1</sup>,

Veriler sulbaktam bazlı tedavilerin tigesikline avantajı olduğunu göstermekte (düşük kanıt düzeyi- ESCMID)

- 386
- İmi
- Tig
- 30 g
- hastanede kalış süresinde fark yok
- Mikrobiyolojik yanıt tigesiklin kolunda **düşük**

- Klinik yanıt ve mortalite de fark yok
- Mikrobiyolojik yanıt tigesiklin kolunda **düşük**

# Kombinasyon mu? Monoterapi mi?

NEJM  
Evidence

Published December 6, 2022  
NEJM Evid 2022; 2 (1)  
DOI: 10.1056/EVIDo2200131

ORIGINAL ARTICLE

## Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms

Keith S. Kaye, M.D., M.P.H.,<sup>1</sup> Dror Marchaim, M.D.,<sup>2</sup> Yisaru Thamilikattu, M.D.,<sup>3</sup> Yehuda Carmeli, M.D.,<sup>4</sup> Cheng-Hsun Chiu, M.D., Ph.D.,<sup>5</sup> George Daikos, M.D.,<sup>6</sup> Sorabh Dhar, M.D.,<sup>7</sup> Emanuele Durante-Mangoni, M.D.,<sup>8</sup> Achilles Gikas, M.D.,<sup>9</sup> Anastasia Kotanidou, M.D.,<sup>10</sup> Mical Paul, M.D.,<sup>11</sup> Emmanuelle Rouïdes, M.D.,<sup>12</sup> Michael Rybak, Pharm.D., Ph.D.,<sup>13</sup> Michael Samarkos, M.D.,<sup>14</sup> Matthew Sims, M.D.,<sup>15</sup> Dora Tancheva, M.D.,<sup>16</sup> Sotirios Tsiodras, M.D.,<sup>17</sup> Daniel Kett, M.D.,<sup>18</sup> Gopi Patel, M.D.,<sup>19</sup> David Caffee, Laura Power, M.D.,<sup>20</sup> Sylvia Munoz-Price, M.D.,<sup>21</sup> Kurt Stevenson, M.D.,<sup>22</sup> Lai Christine Chiou, M.D.,<sup>23</sup> George W. Dhine, Ph.D.,<sup>24</sup> Yarduhi Ghazaryan, M.D.

Epidemiol. Infect. (2023), 141, 1214–1222. © Cambridge University Press 2022  
doi:10.1017/S095026882200194X

### Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant *Acinetobacter baumannii* ventilator-associated pneumonia

H. AYDEMİR<sup>1\*</sup>, D. AKDUMAN<sup>1</sup>, N. FİSKİN<sup>1</sup>, F. COMERT<sup>1</sup>, E. HORUZ<sup>1</sup>,  
A. TERZİP<sup>1</sup>, F. KOKTURK<sup>2</sup>, T. ÖRNEK<sup>3</sup> AND G. CELEBİ<sup>1</sup>

<sup>1</sup> Balıkesir Evren University Medical Faculty, Department of Infectious Diseases and Clinical Microbiology.

## 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,<sup>1</sup> George L. Daikos,<sup>2</sup> Emanuele Durante-Mangoni,<sup>3</sup> Dapha Yohou,<sup>4</sup> Yehuda Carmeli,<sup>5</sup> Yael Dishon Benatrat,<sup>6</sup> Anna Siciu,<sup>7</sup> Roberto Andini,<sup>8</sup> Noa Eliekim-Ritz,<sup>9</sup> Amir Mutman,<sup>10</sup> Ottem Zommer,<sup>11</sup> Anastasia Antoniadou,<sup>12</sup> Pia Clara Prufurd,<sup>13</sup> Amos Adler,<sup>14</sup> Vasko Dickstein,<sup>15</sup> Ioannis Pivkas,<sup>16</sup> Rose Zampino,<sup>17</sup> Václav Datoch,<sup>18</sup> Roni Bitterman,<sup>19</sup> Hiko Zayzoyd,<sup>20</sup> Fikri Koppel,<sup>21</sup> Inbar Levi,<sup>22</sup> Tonya Babich,<sup>23</sup> Lena E. Friberg,<sup>24</sup> John W. Meunier,<sup>25</sup> Ursula Theuretzbacher,<sup>26</sup> Leonard Leibovici

Summary

## 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

Emanuele Durante-Mangoni,<sup>1</sup> Giuseppe Signoriello,<sup>2</sup> Roberto Andini,<sup>1</sup> Annunziata Motta,<sup>3</sup> Maria De Cristoforo,<sup>4</sup> Patrizia Marano,<sup>5</sup> Mattia Bassotti,<sup>1\*</sup> Paolo Malacarne,<sup>6</sup> Nicola Petrosillo,<sup>7</sup> Nicola Gallo,<sup>8</sup> Paola Moccaverio,<sup>9</sup> Antonio Corcione,<sup>10</sup> Claudio Viscoli,<sup>11</sup> Raffaele Zarrilli,<sup>12</sup> Ciro Gallo,<sup>13</sup> and Riccardo Iribi<sup>14</sup>



Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

Journal homepage: [www.elsevier.com/locate/jgar](http://www.elsevier.com/locate/jgar)

## Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant *Acinetobacter baumannii*: A randomised controlled trial

Hye Jung Park<sup>1</sup>, Jae Hwa Cho<sup>2</sup>, Hyung Jung Kim<sup>3</sup>, Sang Hoon Han<sup>3</sup>, Seok Hoon Jeong<sup>4,\*</sup>, Min Kwang Byun<sup>2,5</sup>

- Aslında çalışmaların çoğunda kombinasyon monoterapiye üstün değil
- Sadece 1 çalışma dışında
- kombinasyon kolunda yüksek doz ampisilin-sulbaktam olan



# Monoterapiyi Destekleyen Verilerin Kısıtlılıkları

Hastalar heterojen  
ve sayı kısıtlı

Enfeksiyöz  
kaynaklar deęişken

Kolonizasyonların  
dahil edilmesi

Antibiyotikler ve  
dozlar farklı, tedavi  
kolları arasındaki  
dengesizlikler



# Kombinasyon tedavilerinin yeri



# Polimiksin ve karbapenem kombinasyonu

## 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 I Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yoel Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yacov Dickstein, Ioannis Pivless, Rosa Zampino, Vened Daitch, Roni Biterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzhacher, Leonard Leibovici

Summary

406 hasta; %77 A.baumannii Klinik yanıtta benzer sonuçlar Kombinasyon kolunda artan diyare ve nefrotoksisite

NEJM  
Evidence

Published December 6, 2022

NEJM Evid 2022; 2 (1)

DOI: 10.1056/EVIDoa2200131

ORIGINAL ARTICLE

## Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms

Keith S. Kaye, M.D., M.P.H.,<sup>1</sup> Dror Marchaim, M.D.,<sup>2</sup> Visanu Thamilkikutl, M.D.,<sup>3</sup> Yehuda Carmeli, M.D.,<sup>4</sup> Cheng-Hsun Chiu, M.D., Ph.D.,<sup>5</sup> George Daikos, M.D.,<sup>6</sup> Sorabh Dhar, M.D.,<sup>7</sup> Emanuele Durante-Mangoni, M.D.,<sup>8</sup> Achilles Gikas, M.D.,<sup>9</sup> Anastasia Kotanidou, M.D.,<sup>10</sup> Mical Paul, M.D.,<sup>11</sup> Emmanuelle Roilides, M.D.,<sup>12</sup> Michael Rybak, Pharm.D., Ph.D.,<sup>13</sup> Michael Samarkos, M.D.,<sup>14</sup> Matthew Simms, M.D.,<sup>15</sup> Dora Tancheva, M.D.,<sup>16</sup> Sotirios Tsiodras, M.D.,<sup>17</sup> Daniel Kett, M.D.,<sup>18</sup> Gopi Patel, M.D.,<sup>19</sup> David Calfee, M.D.,<sup>20</sup> Leonard Leibovici, M.D.,<sup>21</sup> Laura Power, M.D.,<sup>22</sup> Sylvia Munoz-Price, M.D.,<sup>23</sup> Kurt Stevenson, M.D.,<sup>24</sup> Laura Susick,<sup>25</sup> Katie Latack,<sup>25</sup> Jolene Daniel,<sup>1</sup> Christine Chiu, M.D.,<sup>26</sup> George W. Divine, Ph.D.,<sup>25</sup> Varduhi Ghazaryan, M.D.,<sup>26</sup> and Jason M. Pogue, Pharm.D.<sup>27</sup>

464 hasta; %78 A.baumannii Klinik yanıt, mikrobiyolojik kür, mortalite de benzer sonuçlar

# Polimiksin ve karbapenem kombinasyonu

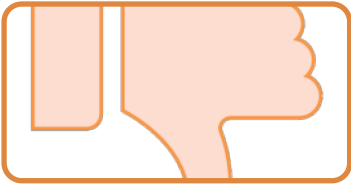


İn vitro sinerjistik etki

Klinik fayda monoterapiye üstün değil



Artmış  $\beta$ -laktam toksisitesine neden olabilir



KRAB tedavisinde yüksek doz, uzun infüzyon meropenem veya imipenem önerilmemekte (IDSA, ESCMID)



Meropenem MIC<8 ise yüksek doz uzun infüzyon kombinasyonda kullanılabilir (ESCMID)

# Polimiksin ve karbapenem kombinasyonu



İn vitro sinerjistik etki

- İn vivo klinik fayda monoterapiye üstün değil

**DO NOT USE**



Meropenem MIC<8 ise yüksek doz uzun infüzyon kombinasyonda kullanılabilir (ESCMID)

# Rifamisinlerin rolü



Bakteriyel protein sentez inhibisyonu



Rifamisinler; hem in vitro hem de hayvan çalışmalarında A. baumannii'ye karşı güçlü aktiviteye sahip



Sinerji; Polimiksinler bakteriyel membran geçirgenliğini bozar, rifamisinin hücre içi penetrasyonu artar, bakteriyel protein sentez inhibisyonu

# Rifamisinlerin rolü



Bakteriyel protein sentez inhibisyonu

Rifamisinlerle ilişkili toksisiteler ve ilaç etkileşimleri  
Klinik çalışmalarda bir faydanın bulunmaması  
Rifamisinlerin KRAB tedavisinde kullanılması önerilmiyor  
(IDSA,ESCMID)



Sinerji; Polimiksinler bakteriyel membran geçirgenliğini bozar, rifamisinin hücre içi penetrasyonu artar, bakteriyel protein sentez inhibisyonu



# Aminoglikozidler



KRAB infeksiyonunda, mevcut seçeneklerden (polimiksin, **AG**, tigesiklin veya sulbaktam kombinasyonları) iki in vitro aktif antibiyotiđi içeren kombinasyon tedavisi (ESCMID)



Ancak spesifik kombinasyon?



Çalışmalarda AG'yi içeren kombinasyonların mortalite üzerine etkisi benzer

# Diđer Kombinasyonlar

Kolistin+vankomisin vs.  
kolistin monoterapi;

Benzer klinik sonuç  
Nefrotiksisite kombinasyonda yüksek

Kolistin+glikopeptid vs.  
kolistin bazlı tedaviler;

Benzer klinik sonuç

Kolistin+fosfomisin vs  
kolistin monoterapi;

Fosfomisin önerilmiyor (IDSA,ESCMID)  
İntrensek dirençli  
Fayda gösterilmemiş

# Nebülize antibiyotikler



Journal of  
Antimicrobial  
Chemotherapy

*J Antimicrob Chemother* 2010; **65**: 2645 – 2649  
doi:10.1093/jac/dkq360 Advance Access publication 28 September 2010

## Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

Pinyo Rattanaumpawan, Jintana Lorsutthitham, Puangpaka Ungprasert, Nasikarn Angkosekwina and Visanu Thomlikitkul\*

Meta-Analysis > *Sci Rep.* 2021 Mar 26;11(1):6969. doi: 10.1038/s41598-021-86342-8.

## Amikacin nebulization for the adjunctive therapy of gram-negative pneumonia in mechanically ventilated patients: a systematic review and meta-analysis of randomized controlled trials

Ding Qin<sup>1</sup>, Hui-Bin Huang<sup>2</sup>, Hua Zhou<sup>1</sup>, Yuan Zhu<sup>1</sup>, Yuan Xu<sup>1</sup>, Bin Du<sup>3</sup>

- Kolistin, amikasin, fosfomisin nebül denenmiş
- Fayda gösterilmemiş
- Bronkokonstriksiyon gibi komplikasyonlara ilişkin endişeler
- Nebülize antibiyotikler önerilmemekte (IDSA, ESCMID)

Randomized Controlled Trial > *Lancet Infect Dis.* 2020 Mar;20(3):330-340.

doi: 10.1016/S1473-3099(19)30574-2. Epub 2019 Dec 19.

## Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial

Michael S Niederman<sup>1</sup>, Jeff Alder<sup>2</sup>, Matteo Bassetti<sup>3</sup>, Francis Boateng<sup>4</sup>, Bin Cao<sup>5</sup>, Kevin Corkery<sup>6</sup>, Rajiv Dhand<sup>7</sup>, Keith S Kaye<sup>8</sup>, Robert Lawatschek<sup>9</sup>, Patrick McLeroth<sup>10</sup>, David P Nicolau<sup>11</sup>, Chen Wang<sup>5</sup>, G Christopher Wood<sup>12</sup>, Richard G Wunderink<sup>13</sup>, Jean Chastre<sup>14</sup>

Clinical Trial > *Chest.* 2017 Jun;151(6):1239-1246. doi: 10.1016/j.chest.2016.11.026.

Epub 2016 Nov 24.

## A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia: IASIS Trial

Marin H Kollef<sup>1</sup>, Jean-Damien Ricard<sup>2</sup>, Damien Roux<sup>2</sup>, Bruno Francois<sup>3</sup>, Beni Ischaki<sup>4</sup>, Zsolt Rozgonyi<sup>5</sup>, Thierry Boulain<sup>6</sup>, Zsolt Ivanyi<sup>7</sup>, Gál János<sup>7</sup>, Denis Garot<sup>8</sup>, Firas Koura<sup>9</sup>, Epaminondas Zakynthinos<sup>10</sup>, George Dimopoulos<sup>11</sup>, Antonio Torres<sup>12</sup>, Wayne Danker<sup>13</sup>, A Bruce Montgomery<sup>14</sup>

# Nebülize antibiyotikler



Journal of  
Antimicrobial  
Chemotherapy

J Antimicrob Chemother 2010; 65: 2645 - 2649  
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Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by Gram-negative bacteria

Pinyo R, Manuamnuay P, Jitana L, Suthitham B, Sornratana U, Harnpanit N, Narkorn A, Kanchanadit P

Meta-Analysis > Sci Rep. 2021 Mar 26;11(1):6969. doi: 10.1038/s41598-021-86342-8.

Amikacin nebulization for the adjunctive therapy of gram-negative pneumonia in mechanically ventilated patients: a systematic review and meta-analysis of randomized controlled trials

**DO NOT USE**

- 
- 
- 
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Epub 2016 Nov 24.

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# Sefiderokolün rolü

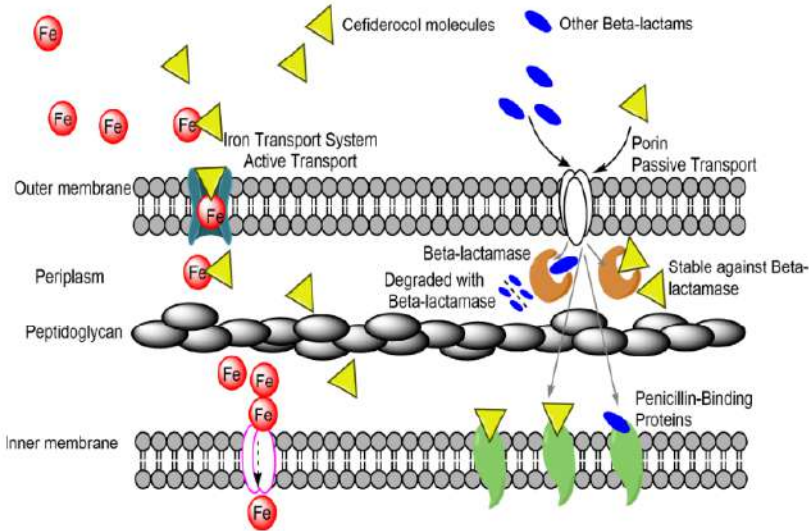


Figure 2. Novel mechanism of action for cefiderocol.

- Gram (-) etkin siderofor sefalosporin
  - $\beta$ -laktamlar porinlerden pasif difüzyon ile
  - Sefiderokol demir transport sistemlerini de kullanır
- KRAB'a karşı in vitro aktif
- Ekim 2019 İYE tedavisinde FDA onaylı
- Eylül 2020 VIP tedavisinde FDA onaylı

# Sefiderokol faz 3 alıřmaları



**Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial**

*Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L. Paterson, Simon Portsmouth, Julian Torre-Gisneros, Kiichiro Toyozumi, Richard G Wunderink, Tsutae D Nagata*

- KRAB infeksiyonu ile
- 54 hasta
- Sefiderokol ve mevcut en iyi tedavi kolları (buyk lde polimiksin bazlı )
- Mortalite sefiderokol kolunda yksek %49 - %18



**Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial**

*Richard G Wunderink, Yuko Matsunaga, Mari Ariyasu, Philippe Clevenbergh, Roger Echols, Keith S Kaye, Marin Kollef, Anju Menon, Jason M Pogue, Andrew F Shorr, Jean-Francois Timsit, Markus Zeitlinger, Tsutae D Nagata*

- Sefiderokol – yksek doz meropenem infzyonu
- iki tedavi rejimi arasında klinik sonularda hibir fark bulunmamıř



# Sefiderokol faz 3 alıřmaları

  Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre,

Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3,

Diđer tedavilere diren veya intolerans durumunda  
Kombinasyon olarak kullanılmalı (IDSA)

tyl tedavi kolonları (büyük ölçüde polimiksin bazlı )  
•Mortalite sefiderokol kolunda yüksek %49 - %18

- iki tedavi rejimi arasında klinik sonuçlarda hiçbir fark bulunmamış

# Sefiderokol faz 3 alıřmaları

**NOT  
AVAILABLE**

Ülkemizde yok

Diđer tedavilere diren veya intolerans durumunda  
Kombinasyon olarak kullanılmalı (IDSA)

• Mortalite sefiderokol  
kolunda yüksek %49 - %18

- iki tedavi rejimi arasında  
klinik sonuçlarda hiçbir  
fark bulunmamış

# Sulbaktam-durlobaktam



Sulbaktam  $\beta$ -laktamaz inhibitörü  
A. baumannii' ye direk etkili

Durlobaktam, sulbaktamı diđer  $\beta$ -laktamazlardan koruyor

Ambler klas A, C ve D'ye etkili  
Metallo  $\beta$ -laktamazlara etkili deđil

FDA mayıs 2023'te ViP için onayladı

# Sulbaktam-durlobaktam faz 3 alıřması

Clinical Trial > Lancet Infect Dis. 2023 Sep;23(9):1072-1084. doi: 10.1016/S1473-3099(23)00184-6.

Epub 2023 May 11.

**Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii*–calcoaceticus complex: a multicentre, randomised, active–controlled, phase 3, non–inferiority clinical trial (ATTACK)**

Keith S Kaye <sup>1</sup>, Andrew F Shorr <sup>2</sup>, Richard G Wunderink <sup>3</sup>, Bin Du <sup>4</sup>, Gabrielle E Poirier <sup>5</sup>, Khurram Rana <sup>6</sup>, Alita Miller <sup>6</sup>, Drew Lewis <sup>6</sup>, John O'Donnell <sup>6</sup>, Lan Chen <sup>7</sup>, Harald Reinhart <sup>7</sup>, Subasree Srinivasan <sup>8</sup>, Robin Isaacs <sup>6</sup>, David Altarac <sup>6</sup>

- 16 lke 59 klinik
- 125 hasta KRAB kan dolařım infeksiyonu ve VİP
- İmipenem+SUL-DUR
- İmipenem+kolistin
- Mortalite daha dřk (%19-%32)
- Klinik yanıt daha yksek (%61-%40)
- Mikrobiyolojik yanıt daha iyi (%68-%41)

# Sulbaktam-durlobaktam faz 3 çalışması

**NOT  
AVAILABLE**

Ülkemizde yok

- 16 ülke 59 klinik
- 125 hasta KRAB kan dolaşım infeksiyonu ve VIP
- İmipenem+SUL-DUR
- İmipenem+kolistin
- Mortalite daha düşük (%19-%32)
- Klinik yanıt daha yüksek (%61-%40)
- Mikrobiyolojik yanıt daha iyi (%68-%41)

Clinical Trial > Lancet Infect Dis. 2023 Sep;23(9):1072-1084. doi: 10.1016/S1473-3099(23)00184-6.

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# Sonuç olarak.. Her iki kılavuzda



## **Öneriyor**

Yüksek doz sulbaktamı

Klinik iyileşmeye kadar  
kombinasyon (polimiksin, tigesiklin,  
aminoglikozid, sefiderokol)



## **Önermiyor**

Karbapenem+kolistin

Fosfomisin, rifampin

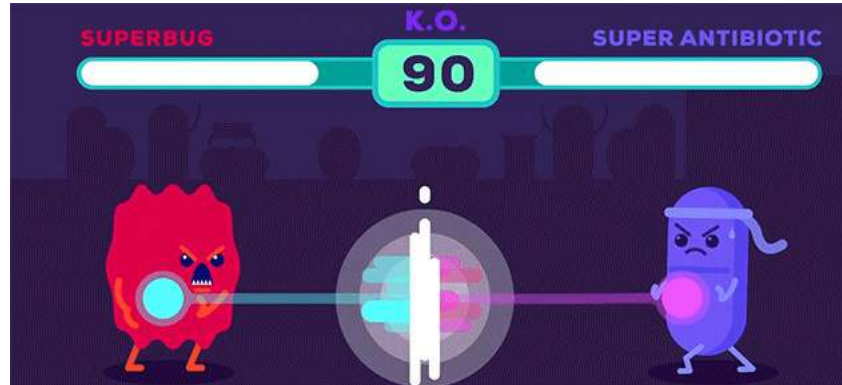
Nebülize antibiyotik



# Sonuç olarak..

Sulbaktam-durlobaktam umut verici, ancak heterorezistan suşlar??

Sefiderokol sonuçları eldeki tedavilerle benzer, direnç ...





**KLİNİK DİRENÇLİ GRAM  
NEGATİF ÇOMAK  
İNFEKSİYONLARINDA TANI  
VE TEDAVİ REHBERİ**



**BEKLEYİN..**



**YÜKLENİYOR..**

**Teşekkürler..**