Dirençli Non-fermentatiflerde Farklı Kombinasyonlar

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Non-fermentatif mikroorganizmalar

- Çoklu ilaç dirençli non-fermentatif basiller sağlık hizmetiyle ilişkili infeksiyonlarda özellikle yoğun bakım birimlerinde ciddi sorunlar oluşturan ve sık rastlanan etkenlerdir

- Çoklu ilaç dirençli *Acinetobacter baumannii*
- Çoklu ilaç dirençli *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*
- *Burkholderia cepecia*
- ….

Direnç: Tanım

İlaç sınıfları: aminoglikozidler, antipseudomonal karbapenemler, antipseudomonal SS'ler (sefepim ve seftazidim), antipseudomonal kinolonlar, antipseudomonal penisilin + ß-laktamaz inhibitörleri (tikarsillin-klavulonik asit ve piperasilin/tazobaktam), monobaktamlar (aztreonam), fosfomisin, polimiksinler

Multidrug Resistance (MDR)
En az 3 veya daha fazla sınıftaki antimikrobiyal ajana dirençli

Extensive (Extreme) Drug Resistance (XDR)
1 veya 2 sınıf dışında kalan tüm antimikrobiyal ajanlara dirençli

Pandrug Resistance (PDR)
Tüm antimikrobiyal ajanlara dirençli, Sulbaktam, polimiksinler ve tigesiklin dahil hepsi

Magiorakos AP. Clin Microbiol Infect. 2012;18:268–281.

Epidemiyoloji

Epidemiyoloji-Avrupa

- The European Centre for Disease Prevention and Control 2011-2012 Point-Prevalence Survey

1) *E. coli* (15.9%),
2) *S. aureus* (12.3%),
3) *Enterococcus* spp. (9.6%),
4) *P. aeruginosa* (8.9%),
5) *Klebsiella* spp. (8.7%),

ECDC; 2013

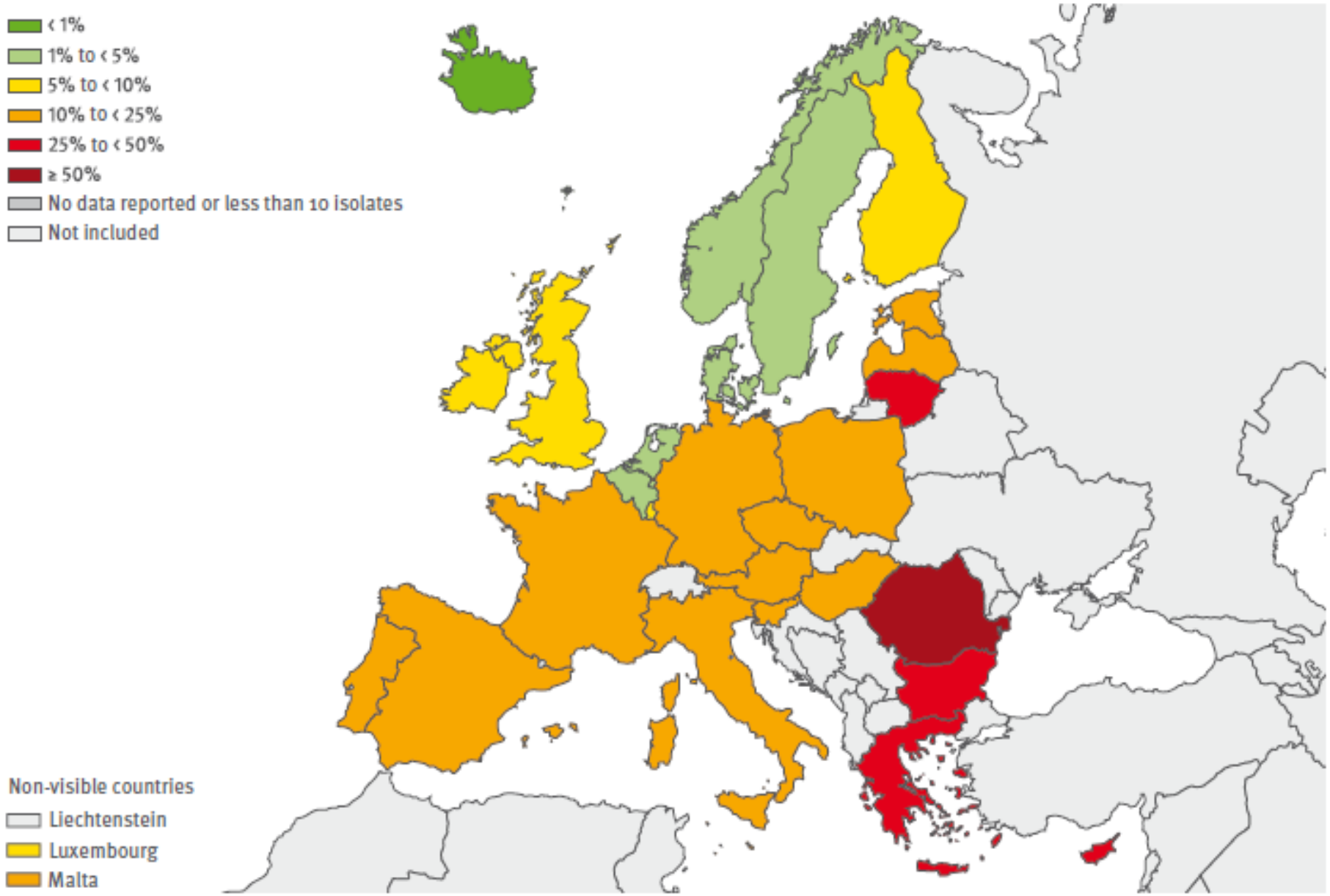
Epidemiyoloji-Avrupa

Table 14. Antimicrobial resistance markers in microorganisms reported in healthcare-associated infections, ECDC PPS 2011–2012

	N of isolates	N with known result	N NS	% NS
Other gram-negative bacteria, CAR-NS				
Pseudomonas aeruginosa, CAR-NS	878	756	240	31.8
Acinetobacter baumannii, CAR-NS	316	292	237	81.2

ECDC; 2013

Figure 5.35: *Pseudomonas aeruginosa*: proportion of invasive isolates resistant to carbapenems in 2010



Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014

TABLE 4. Distribution and Rank Order of Pathogens Frequently Reported to the National Healthcare Safety Network (NHSN), by Type of Healthcare-Associated Infection (HAI), 2011–2014

	Overall		CLABSI		CAUTI		VAP[a]		SSI	
Pathogen	No. (%) of pathogens	Rank[b]	No. (%) of pathogens	Rank[b]	No. (%) of pathogens	Rank[b]	No. (%) of pathogens	Rank[b]	No. (%) of pathogens	Rank[b]
Escherichia coli	62,904 (15.4)	1	5,193 (5.4)	7	36,806 (23.9)	1	476 (5.4)	6	20,429 (13.7)	2
Staphylococcus aureus	48,302 (11.8)	2	12,706 (13.2)	2	2,515 (1.6)	14	2,179 (24.7)	1	30,902 (20.7)	1
Klebsiella (pneumoniae/oxytoca)	31,498 (7.7)	3	8,062 (8.4)	4	15,471 (10.1)	4	898 (10.2)	3	7,067 (4.7)	6
Coagulase-negative staphylococci[c]	31,361 (7.7)	4	15,794 (16.4)	1	3,696 (2.4)	13	72 (0.8)	13	11,799 (7.9)	3
Enterococcus faecalis[d]	30,034 (7.4)	5	8,118 (8.4)	3	10,728 (7.0)	5	32 (0.4)	21	11,156 (7.5)	4
Pseudomonas aeruginosa	29,636 (7.3)	6	3,881 (4.0)	10	15,848 (10.3)	3	1,449 (16.5)	2	8,458 (5.7)	5
Candida albicans[d]	27,231 (6.7)	7	5,761 (6.0)	6	17,926 (11.7)	2	193 (2.2)	10	3,351 (2.2)	12
Enterobacter spp.[c]	17,235 (4.2)	8	4,204 (4.4)	9	5,689 (3.7)	9	727 (8.3)	4	6,615 (4.4)	8
Enterococcus faecium[d]	14,942 (3.7)	9	6,567 (6.8)	5	4,212 (2.7)	11	23 (0.3)	24	4,140 (2.8)	11
Other *Enterococcus* spp.[d]	14,694 (3.6)	10	1,974 (2.0)	14	6,291 (4.1)	7	19 (0.2)	27	6,410 (4.3)	9
Proteus spp.[c]	11,249 (2.8)	11	820 (0.8)	17	6,108 (4.0)	8	125 (1.4)	12	4,196 (2.8)	10
Yeast NOS[e]	10,811 (2.6)	12	763 (0.8)	18	9,443 (6.1)	6	54 (0.6)	16	551 (0.4)	25
Other *Candida* spp.[d]	10,641 (2.6)	13	4,730 (4.9)	8	5,178 (3.4)	10	37 (0.4)	19	696 (0.5)	19
Candida glabrata[d]	8,121 (2.0)	14	3,314 (3.4)	11	4,121 (2.7)	12	12 (0.1)	33	674 (0.5)	20
Bacteroides spp.	7,560 (1.9)	15	515 (0.5)	19	2 (<0.1)	130	2 (<0.1)	72	7,041 (4.7)	7
Other pathogen	51,932 (12.7)		14,130 (14.6)		9,771 (6.4)		2,507 (28.5)		25,524 (17.1)	
Total	408,151 (100)		96,532 (100)		153,805 (100)		8,805 (100)		149,009 (100)	

Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014

Selected Antimicrobial Agents, by Period, 2011–2012

	2011[a]			2012[a]		
Pathogen, antimicrobial	No. of isolates reported	% of isolates tested[b]	% Resistance[c]	No. of isolates reported	% of isolates tested[b]	% Resistance[c]
Staphylococcus aureus	1,062			1,117		
OX/METH/CEFOX		96.5	46.1		96.5	42.4
Enterococcus spp.						
E. faecium	13			10		
VAN		84.6	…		100.0	…
E. faecalis	14			18		
VAN		78.6	…		94.4	…
Klebsiella (pneumoniae/oxytoca)	424			474		
ESC4		88.4	23.2		86.3	21.0
Carbapenems		75.9	11.5		75.1	10.1
MDR1		93.6	15.9		93.9	12.8
Escherichia coli	219			257		
ESC4		88.1	15.0		81.7	16.7
FQ3		96.3	38.9		93.4	30.8
Carbapenems		79.5	1.1		69.3	2.2
MDR1		94.5	7.7		92.6	9.7
Enterobacter spp.	338			389		
ESC4		95.6	30.0		93.6	26.9
Carbapenems		76.6	1.9		72.2	3.2
MDR1		95.6	5.3		96.1	2.9
Pseudomonas aeruginosa	702			747		
AMINOS		94.7	23.3		96.9	18.2
ESC2		96.6	29.4		94.8	25.7
FQ2		96.3	31.8		94.0	31.9
Carbapenems		87.3	27.6		81.7	28.4
PIP/ PIPTAZ		83.3	19.1		81.5	19.4
MDR2		98.1	20.8		96.4	19.9
Acinetobacter spp.	287			252		
Carbapenems		85.0	63.5		82.9	55.5
MDR3		98.6	63.3		98.8	53.8

T.C.
SAĞLIK BAKANLIĞI
Halk Sağlığı Genel Müdürlüğü
Bulaşıcı Hastalıklar Dairesi Başkanlığı

ULUSAL
SAĞLIK HİZMETİ İLİŞKİLİ ENFEKSİYONLAR SÜRVEYANS AĞI
ÖZET RAPORU
2017

Temmuz, 2018, ANKARA

Epidemiyoloji-Türkiye

Tablo 25. Türkiye'de Sağlık Hizmeti İlişkili Enfeksiyonlarda Antimikrobiyal Direnç Oranları, 2017.

Antimikrobiyal Direnç Oranları *				
ANTİMİKROBİYAL DİRENÇLİ PATOJEN	**Birim Sayısı †**	**Toplam Etken Sayısı**	**Dirençli Etken Sayısı**	**Ağırlıklı Genel Ortalama**
TÜRKİYE GENELİ				
VRE	286 (91)	3641	443	12.17
MRSA	416 (100)	3166	1.185	37.43
MRKNS	347 (122)	4121	2.612	63.38
Escherichia coli suşlarında ESBL	520 (171)	7916	3.680	46.49
Klebsiella pneumoniae suşlarında ESBL	432 (196)	9610	4.650	48.39
Karbapenem dirençli *Acinetobacter baumannii*	391 (222)	11499	8.102	70.46
Karbapenem dirençli *Pseudomonas aeruginosa*	467 (166)	6632	2.275	34.30
Kolistin dirençli *Acinetobacter baumannii*	391 (222)	11499	551	4.79

Direnç mekanizmaları

Direnç mekanizmaları

- Enzim yapımı
  - Beta laktamazlar
    - Genişletilmiş spektrumlu beta laktamazlar
    - Amp-C beta laktamazlar
    - Serin beta laktamazlar
    - Metallo beta laktamazlar
    - …
  - Aminoglikozid modifiye edici enzimler
- Bağlanma noktasındaki mutasyonlar
- Dış membran proteinlerindeki değişiklikler
- Efluks pompaları

P. aeruginosa

- Efluks sistemleri
  - MexAB-OprM ve MexXY-OprM: İntrensek direnç
  - MexCD-OprJ ve MexEF-OprN: Kazanılmış direnç
- Beta-laktamazlar
  - A sınıfı: TEM-1, PER-1, SHV-12, CTX-M gibi.
    - PER-1 ile seftazidim direnci
  - B sınıfı (MBL): IMP-1, 2, 3, 4, 5, 6, VIM-1, 2, 3
    - Penisilin ve SS direnci
  - Kromozomal beta-laktamaz Amp C:
    - Ampisilin ve çoğu SS'leri hidrolize eder
  - D sınıfı (OXA): Karbapenemlere karşı direnç

P. aeruginosa

- OprD protein kaybı
  - Karbapenem direnci
- Enzimatik modifikasyon
  - Aminoglikozidlere direnç
- Hedef bölge değişikliği
- DNAgiraz mutasyonu
  - Kinolon direnci
- PBP değişikliği

Acinetobacter spp

- Beta-laktamazlar
  - A sınıfı: TEM-1, PER-1, SHV-12, CTX-M gibi.
    - PER-1 ile ampisilin ve sefop-sulbaktam direnci
  - B sınıfı (MBL): IMP-1, 2, 4, 5, 6, SIM-1, VIM-2
    - Aztreonam hariç tüm beta-laktamları hidrolize eder
  - C sınıfı (Amp C):
    - Penisilinleri ve sefepim hariç tüm SS'leri hidrolize eder
  - D sınıfı (OXA): OXA-51 ve OXA-58 ülkemizde mevcut
    - Karbapenemlere karşı direnç

Karbapenem hidrolize eden D grubu B-laktamazlar en fazla saptanan karbapenemazlardır

Acinetobacter spp

- Enzimatik modifikasyon
  - Aminoglikozidlere direnç
- Porin kaybı
  - İmipeneme direnç
- Efluks pompası
  - Beta-laktam, aminoglikozid, kinolon direnci
  - Tigesiklin direnci (AdeABC)
- Lipopolisakkarid yapıdaki modifikasyonlar
  - Kolistin direnci

Risk faktörleri

The risk factors and spread of multidrug-resistant *Acinetobacter baumannii* in intubated patients in a medical intensive care unit

- *A. baumanii* kolonizasyonu için risk faktörleri;
  - APACHE II skoru
  - Entübasyon süresi
  - Diabetes mellitus
  - Yaş
  - Koroner arter hast
  - Protez

- *A. baumanii* infeksiyonu için risk faktörleri;
  - Yatış süresi
  - Trakeostomi
  - Diabetes mellitus
  - *A. baumanii* ile kolonizasyon

Alp E. Turk J Med Sci 2009;39(5):761-769.

Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature

M.E. Falagas [a,b,c,*], P. Kopterides [a,d]

A. baumanii

28 vaka-kontrol çalışması
Önceden antibiyotik kullanımı Karbapenem, 3. kuşak SS
Mekanik ventilasyon
Yoğun bakım yatışı ve süresi
Hastalığın ciddiyeti
Cinsiyet
Bazı girişimler Trakeostomi, hidroterapi

27 kontrollü olmayan çalışma
Çevresel kontaminasyon Solunum ve aspirasyon ekipmanları, ventilatör tüpü, yatak kenarları, lavabo
Kontamine eller
Önceden antibiyotik kullanımı Karbapenem, 3. kuşak SS

J Hosp Infect 2006;64:7-15.

Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature

M.E. Falagas [a,b,c,*], P. Kopterides [a,d]

P. aeruginosa

25 vaka-kontrol çalışması
Önceden antibiyotik kullanımı Karbapenem, kinolon
Mekanik ventilasyon
Yoğun bakımda ve hastanede yatış süresi
Diabetes mellitus
KOAH

17 kontrollü olmayan çalışma
Çevresel kontaminasyon Musluk suyu, su kaynakları,
Kontamine eller
Yoğun bakımda yatış
Önceden antibiyotik kullanımı

J Hosp Infect 2006;64:7-15.

Tedavi Yaklaşımları

Kombinasyon tedavileri tartışmalı bir konu

- Temel teorik avantajları
  - Hızlı bakteriyel öldürme
  - Bakteriyel direnç gelişiminin önlenmesi
  - Sinerjistik veya aditif etkisinin olması
  - İnfeksiyon bölgesinde en az bir antibiyotiğin yeterli konsantrasyona ulaşma olasılığını artırma

Sonuçta tedavi başarısızlığı ve mortalitede azalma hedefleniyor

Kombinasyon tedavileri tartışmalı bir konu

- Sinerji
  - İn vitro sinerji olsa da in vivo gerçekleşmeyebilir
    - Doku veya plazmada yeterli konsantrasyona ulaşmayabilir
  - Test edilen antibiyotiklerden birinde direnç varsa veya MIC düşükse bile sağlanabilir

- Kombinasyon tedavilerinin dezavantajları
  - Yan etkileri ve maliyet artıyor,
  - Antagonizm riski var
    - Örneğin kolistin + tigesiklinde indeferans ve antagonizm gerçekleşebildiği bildirilmiştir

Colistin-based treatment for extensively drug-resistant *Acinetobacter baumannii* pneumonia☆

Thana Khawcharoenporn[a,*], Nattapol Pruetpongpun[a], Pimsiri Tiamsak[b], Sasinuch Rutchanawech[a], Linda M. Mundy[c], Anucha Apisarnthanarak[a]

[a] *Division of Infectious Diseases, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*
[b] *Thammasat University, Pathumthani, Thailand*
[c] *GlaxoSmithKline, Collegeville, PA, USA*

- Retrospektif bir çalışma, XDR-AB pnömonisi olan 236 hasta
- İnfeksiyon Hastalıkları Bölümü tarafından belirlenen aktif rejimler
    1. Inhale Kolistin
    2. IV Kolistin (300 mg yükleme, takiben 12 saatte 150 mg)
    3. Tigesiklin (100 mg yükleme, takiben 50 mg 12 saatte bir)
    4. Yüksek doz sulbaktam (6 gr/gün)
    5. Yüksek doz uzamış infüzyon karbapenem
- Tümü 14 gün

Bunların dışındakiler inaktif rejimler

Int J Antimicrob Agents 2014;43:378-82

Sonuç

- 52 (% 22) hasta uygun tedavi almamış
  - İnfeksiyon Hastalıkları konsultasyonu oranı % 8 (p<0.001)
  - APACHE II skoru daha yüksek (p<0.001)
- 28 günlük sağkalım oranı % 0 (ortalama sağkalım süresi 4 gün)

***

- 3 grup için kolistin bazlı rejim kullanılmış

1. Kol + yüksek doz sulbaktam (% 91'i inhale, % 9'u IV kolistin almış)
2. Kol + tigesiklin (% 93'ü inhale, %7'si IV kolistin almış)
3. Kol + karbapenem (uzun infüzyon, yüksek doz) (% 93'ü inhale, %7'si IV kolistin almış)

Int J Antimicrob Agents 2014;43:378-82

Sonuç

28 günlük sağkalım açısından gruplar arasında fark yok

Table 2
Characteristics and outcomes of 166 patients treated with colistin-based two-drug con

Variable	CL + SB
Outcomes	
Survival at 28 days	
All pneumonia	60 (6
HAP	25/43 (5
VAP	35/50 (7
Mean survival time (days) by log-rank test	
All pneumonia	23
HAP	22
VAP	23
Microbiological cure at the end of therapy	59/70 (8
Median LoS after infection (days) (range)	39 (1
Adverse reactions from treatment regimen [g]	8 (9

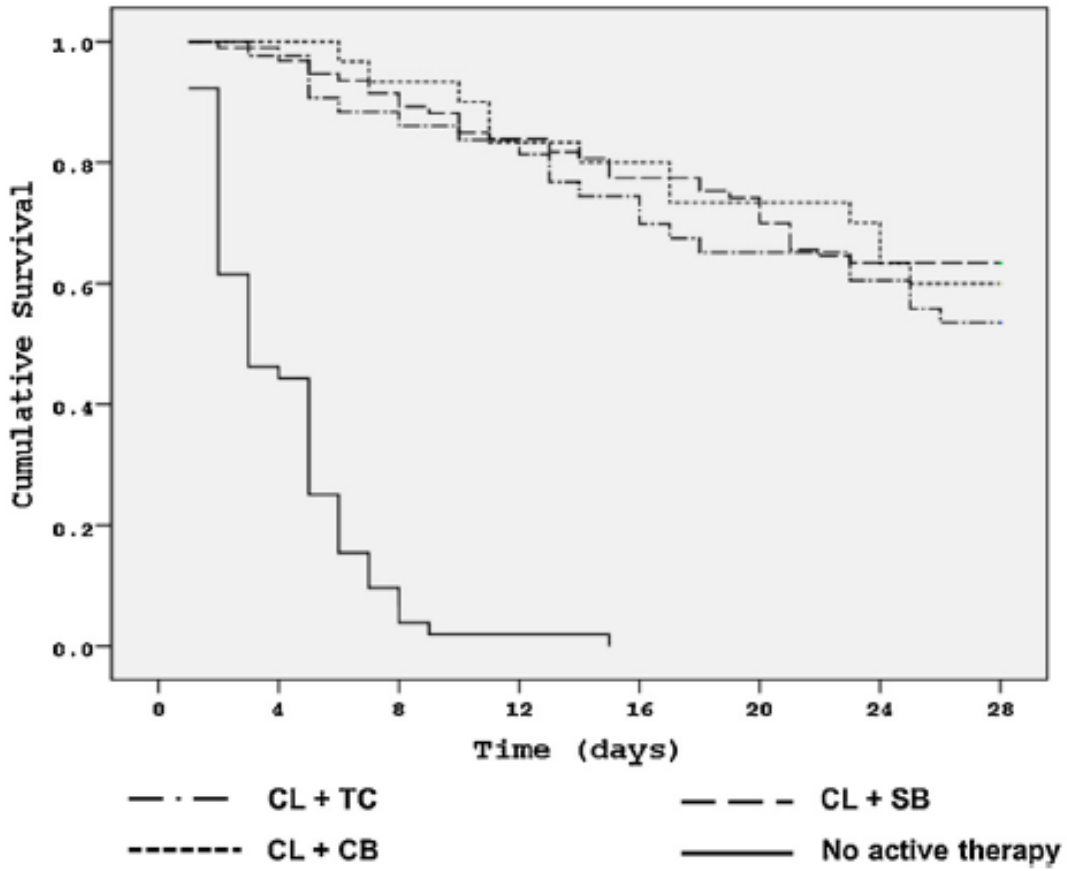


Fig. 1. Kaplan–Meier survival analysis for death at 28 days after the onset of extensively drug-resistant *Acinetobacter baumannii* pneumonia. Comparison between

Int J Antimicrob Agents 2014;43:378-82

- Toplamda 28 günde 125 (% 53) ölüm görülmüş
- Ölenler yaşayanlara kıyaslandığında
  - Yüksek APACHE II skoru olmak,
  - Aktif olmayan ilaç almak,
  - İnfeksiyon Hastalıkları konsültasyonu istenmemek,
  - Malignansisi olmak,
  - KBY'si olmak daha fazla

Int J Antimicrob Agents 2014;43:378-82

Combination therapy for extensively-drug resistant gram-negative bacteria

Ilias Karaiskos [a], Anastasia Antoniadou[b] and Helen Giamarellou [a]

[a]6th Department of Internal Medicine, Hygeia General hospital, Athens, Greece; [b]4th Department of Internal Medicine, National and Kapodistrian University of Athens School of Medicine, University General Hospital ATTIKON, Athens, Greece

- XDR tüm Gram negatif bakterileri değerlendiren bir meta-analiz

Expert Rev Anti-inf Ther 2017;15:1123-40

A. baumanii değerlendiren 17 çalışma var

Table 2. Demographic characteristics of patients included in 17 studies fulfilling the inclusion criteria.

Total number of patients	1.674
Monotherapy arm	785
Combination arm	889
Number of randomized control studies	3 [83,85,86]
Number of prospective observational studies	1 [80]
Number of retrospective observational studies	13 [77–79,81,82,84,87–93]
Age (mean/median)	**Years**
Monotherapy arm	51.7/70.6
Combination arm	61/73
Duration of therapy	**Range-days**
Monotherapy arm	6.3–14
Combination arm	9.8–18
Type of predominant infection[a]	**Number of patients**
Monotherapy arm	645
VAP	450
BSI	195
Combination arm	884
VAP	550
BSI	334
Severe sepsis [81,82]	**Number of patients**
Monotherapy	70
Combination	39
Septic shock [81,82]	**Number of patients**
Monotherapy arm	26
Combination arm	26
Severe sepsis/septic shock[80,93]	**Number of patients**
Monotherapy arm	38
Combination arm	15

Distribution of patients in monotherapy and combination therapy arms	Number of patients	
Combination of polymyxin with:	Monotherapy	combination
Carbapenems – 6 studies: [77,79,84,88,90,92]	170	292
Tigecycline – 4 studies: [80,84,87,91]	181	95
Sulbactam – 4 studies: [82,84,88,90]	128	137
Rifampicin – 3 studies: [83,85,89]	147	237
Fosfomycin – 1 study: [86]	47	47
Aminoglycosides – 1 study: [93]	23	10
Glycopeptides – 2 studies: [78,81]	89	71
Total number of patients	**785**	**889**

Özellikle polimiksin duyarlı, karbapenem dirençli XDR-AB ile gelişen infeksiyonların olduğu çalışmalar

Tüm çalışmalardaki suşlar kolistin duyarlı

Kolistin dozları farklı

Expert Rev Anti-inf Ther 2017;15:1123-40

28 günlük mortalite

Monoterapilerde % 23,5-67,6

Kombinasyon tedavilerinde % 24,2-73

Monoterapiye karşın kombinasyon tedavisinde istatistiksel fark yok

- Monoterapide
  - Klinik kür oranı: %29,8-87
  - Mikrobiyolojik kür: %22-72,3
- Kombinasyon tedavilerinde
  - Klinik kür oranı: %40-81,2
  - Mikrobiyolojik kür: %35-100

Fark sadece iki çalışmada anlamlı

Expert Rev Anti-inf Ther 2017;15:1123-40

RKÇ yok

Az sayıda hasta içeren az sayıda çalışma var

P.aeruginosa'yı değerlendiren 5 çalışma var

Table 3. Clinical evidence comparing polymyxin/colistin monotherapy to combination therapy in infections due to MDR/XDR *Pseudomonas aeruginosa*.

Ref.	Year	Study	Setting	Number of patients with MDR PA or CRPA	Type of infection	Monotherapy (no)	Combination therapy (no)	Result/outcome
[105]	2003	Prospective cohort	ICU (SOT)	23	Pneumonia Intra-abdominal	Colistin (10)	Amikacin (4) Antipseudomonal b-lactam (9)	No difference in favorable outcome (resolution of symptoms by the end of therapy without death)
[106]	2007	Retrospective	ICU	74	VAP	Polymyxin B (46)	Imipenem (24) b-lactam (2) Ciprofloxacin (2)	No difference in favorable outcome (resolution of symptoms by the end of therapy)
[78]	2014	Retrospective	ICU	31	VAP, BSI	Colistin (14)	Glycopeptide (5) or antipseudomonal drug (7) or both (5)	No difference in 30-day mortality Colistin-Glycopeptide combination for ≥5 days a protective factor for mortality in multivariate analysis
[107]	2014	Retrospective	Hematology-Oncology	15	Bacteremia	Colistin (8)	Not mentioned (7)	No difference in mortality during the episode (37.5% for monotherapy and 57.1% for combination therapy, $p = 0.8$)
[92]	2015	Retrospective	ICU	18	VAP, BSI	Polymyxin B (15)	Carbapenem (3)	Significant difference in 30-day mortality between monotherapy (93.3%) and combination therapy (0%) for Pseudomonal infections and the overall

Tamamen sınırlı ve düşük kalitede klinik kanıtlar CRPA tedavisi için kombinasyon tedavisinin kullanımını desteklememektedir

Expert Rev Anti-inf Ther 2017;15:1123-40

Clinical Experience of Colistin-Glycopeptide Combination in Critically Ill Patients Infected with Gram-Negative Bacteria

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- Kolistin ile glikopeptid kombinasyonunu 5 günden fazla alan hastalarda kombinasyon tedavisinin 30.gün mortalitesinde koruyucu bir etkisi olduğu saptanmış
- Nefrotoksisite oranı düşük
  - Glikopeptid alanlarla almayanlar arasında fark yok
- En az 5 gün kolistin ve glikopeptid kombinasyonunun tüm hastalarda ve MDR-AB infeksiyonu olan hastalarda bağımsız olarak daha iyi sonuçlarla beraber

Antimicrob Agent Chemother 2014;58:851-858

Sonuç-yorum

- Çoğu heterojen, retrospektif temelli,
- Düşük-çok düşük kalitede çalışmala

- AB için;
  - Kombinasyon … avantaj sağlamıyor
  - Ancak … eptik şok ve sınırda MIC'e sahip izolatlarla … binasyon tedavisi tavsiye edilebilir
- *P.ae…*
  - Kon… tedavisinin gerekliliği ile ilgili minimal ve yetersiz veri mevcut

Bu konuda iyi planlanmış RKÇ'lara acil ihtiyaç var
Kliniği ciddi hastalarda gereksiz kombinasyonlardan kaçınmak,
salgınlara yol açmamak, akabinde endemik hale getirmemek için

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Active monotherapy and combination therapy for extensively drug-resistant *Pseudomonas aeruginosa* pneumonia

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- XDR-PA infeksiyonlarında monoterapiye karşın kombinasyon tedavi
- 6 yıllık, retrospektif
- 3 grup tedavi kolu var
    1. Aktif ilaç almayan (n:22)
    2. Aktif monoterapi grubu (n:74)
    3. Aktif iki ilaçla kombine terapi (n:40)
- Toplam 136 hasta
    - %37'si VİP

Int J Antimicrobiol Agents 2018;52:828–834

Verilen ilaçlar

Table 1
Antibiotics used in each treatment group.

Active monotherapy (n=74)	Active combined two-drug therapy (n=40)	Inactive therapy (n=22)
Colistin and non-active carbapenem (n=40; 54%)	Colistin and fosfomycin (n=22; 55%)	Piperacillin-tazobactam (n=10; 46%)
Colistin alone (n=22; 30%)	Doripenem[a] and fosfomycin (n=12; 30%)	Non-active carbapenems (n=10; 46%)
Colistin and non-active fosfomycin (n=6; 8%)	Colistin and doripenem[a] (n=6; 15%)	Non-active fosfomycin and non-active carbapenems (n=2; 9%)
Fosfomycin and non-active carbapenem (n=4; 5%)		
Doripenem[a] and non-active fosfomycin (n=2; 3%)		

[a] Doripenem 1 g intravenously for 4 h every 8 h (prolonged infusion) when the minimum inhibitory concentration of *Pseudomonas aeruginosa* was 4–8 mg/L [14].

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28 günde sağkalım ve mikrobiyolojik kür kombinasyon tedavisinde daha yüksek

Table 3
Treatment characteristics and outcomes of extensively drug-resistant *Pseudomonas aeruginosa* pneumonia categorized by a definite treatment regimen.

Variables	All (n=136)	Active monotherapy(n=74)	Active combined two-drug therapy(n=40)	Inactive therapy(n=22)	P-value[a]
Treatment characteristics					
Time to receipt of the active therapy[b] (h, median, IQR)	72 (48–96)	72 (48–96)	60 (48–120)	–	0.30
Infectious diseases consultation	98 (72)	58 (78)	40 (100)	0 (0)	<0.001
Colistin use	92 (68)	66 (89)	26 (65)	0 (0)	<0.001
Intravenous colistin	54/92 (59)	38/66 (58)	16/26 (61)	–	0.73[c]
Nebulized colistin	38/92 (41)	28/66 (42)	10/26 (39)	–	<0.001
Outcomes					
Survival at 28 days					
All pneumonia	74 (54)	38 (51)	36 (90)	0 (0)	<0.001
HAP	42/86 (49)	18/42 (43)	24/26 (92)	0/18 (0)	0.007
VAP	32/50 (64)	20/32 (63)	12/14 (86)	0/4 (0)	<0.001
Survival at 14 days	86 (68)	48 (65)	36 (90)	2 (9)	<0.001
Mean survival time by log rank test (days)					
All pneumonia	20	20	26	8	<0.001
HAP	19	19	27	8	0.001
VAP	21	22	25	8	<0.001
Microbiological cure at the end of therapy	76 (56)	40 (54)	36 (90)	0 (0)	0.11
Adverse reaction					
Nephrotoxicity	16 (12)	12 (16)	4 (10)	0 (0)	0.09
Diarrhoea	2 (2)	0 (0)	2 (5)	0 (0)	<0.001

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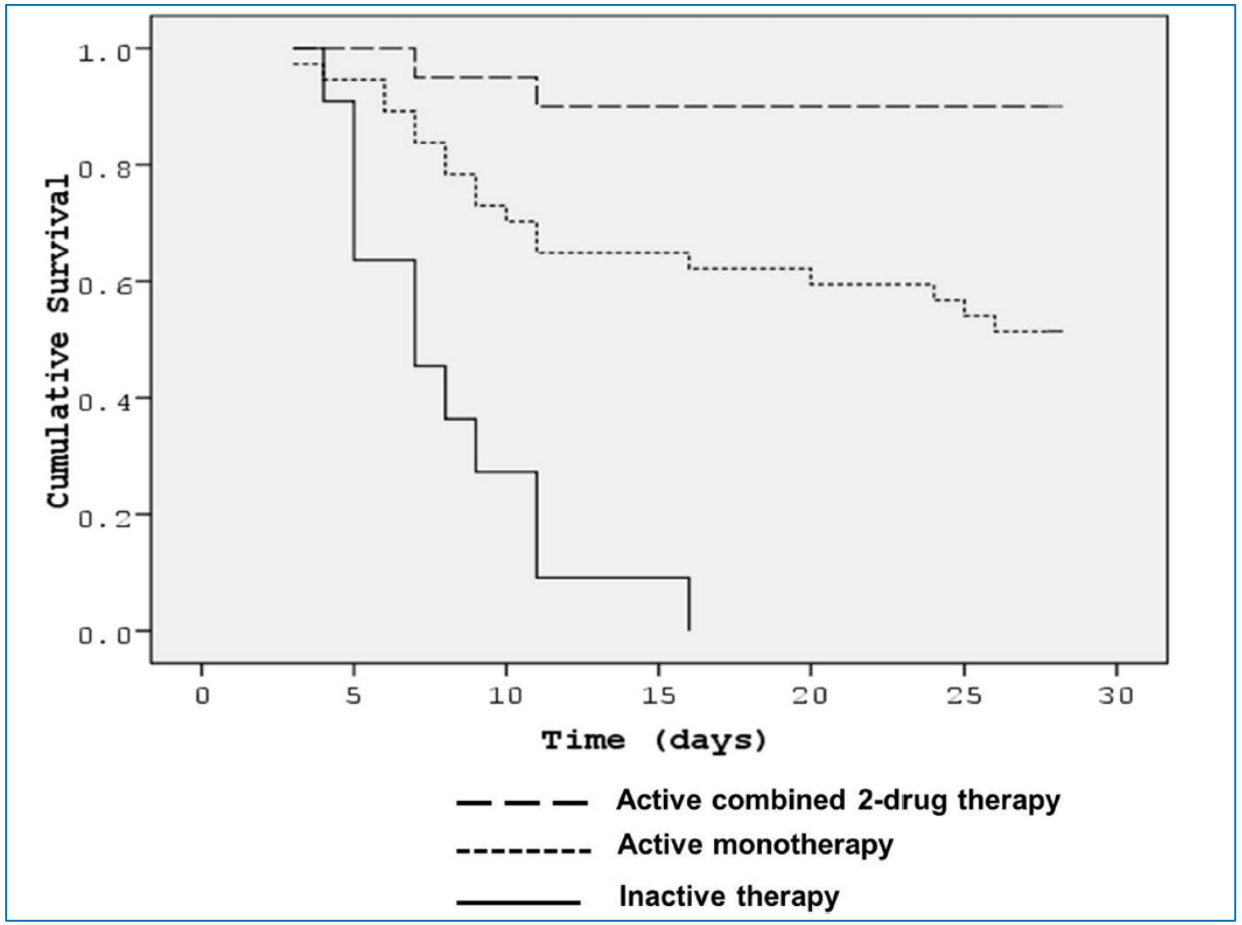

Mortalite için risk faktörleri

Model 1: all patients
Receipt of inactive therapy
No infectious diseases consultation

Model 2: patients who received at least one active drug against XDR-PA
Receipt of active monotherapy (vs active combined two-drug therapy)
No infectious diseases consultation

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Intravenous colistin combination antimicrobial treatment vs. monotherapy: a systematic review and meta-analysis

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- 32 makale
- Genel olarak makalelerin kalitesi düşük-çok düşük olarak değerlendirilmiş
- Kolistin dozu, yükleme, kombinasyon antibiyotikleri çok farklı
- 3 RKÇ var
  - AB'de kolistin monoterapisi ile kolistin + rifampisin veya kolistin + fosfomisin arasında belirgin bir fark olduğunu göstermede başarısız

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Table 1
Characteristics of studies providing data for colistin combination therapy vs colistin monotherapy.

Author/year of publication (reference)	Region/ study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of study or Col-treated patients (Col mono/Col combo)	Mean/median IV Col dose (MIU/24 h)[a,b]	Ratio of mean/ median Col dose to highest dose[c]	Activity of antibiotic combination[d]	Renal impairment (baseline) (% of study or Col-treated population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Batirel 2014	Turkey/ 2009–2012	Retrospective cohort	BSI and CR-BSI (100)	XDR *Acinetobacter* spp. (100)	250 (36/214)	9[e,k]	1	NR	NR	NR	Mean APACHE II score: Col mono: 17.9 (±7.1), Col combo: 18.6 (±6.9)
Aydemir 2013	Turkey/ 2011–2012	RCT	VAP (100)	Carb-R *A. baumannii* (100)	43 (22/21)	Median: 9[f,l]	1	Rif: active (32.5% of the isolates were I/R)	CRF (9)	100	Mean APACHE II score: Col mono: 18 (±4.9), Col combo: 20.1 (±6.8)
Simsek 2012	Turkey/ 2008–2011	Retrospective case–control	VAP (70.5), BSI (12), other (17.5)	COS *A. baumannii* (100)	51 (20/31)	3–9[e,l]	0.33–1	NR	ARF–CRF (4)	At least 90.19%	APACHE II score: 17.73 (±6.24) (range 5–32)
Falagas 2009	Greece/ 2000–2007	Retrospective cohort	Pneumonia (60), BSI (13), IAI (9), CR-BSI (6), other (12)	MDR Gram-negative (COS 52.3): *A. baumannii* (66), *P. aeruginosa* (26), *K. pneumoniae* (7), *S. maltophilia* (0.5), *E. cloacae* (0.5)	258 (36/222)	≤3–9	≤0.33–1	NR	CRF: study: (5)	For study patients: 86	Mean APACHE II score: 17 (range 2–39)
Durante-Mangoni 2013	Italy/ 2008–2011	RCT	VAP (69), BSI (20), HAP (9), cIAI (2)	XDR *A. baumannii* (100)	209 (105/104)	6[m]	0.66	Rif: active (24% of the isolates R)	CRF (50), ESRD (17)	100	NR
Lim 2011	Korea/ 2000–2007	Retrospective cohort	BSI (100)	MDR *Acinetobacter* spp. (100)	Overall: 70, Col-treated: 31 (20/11)	4.5–9[e,l]	0.5–1	NR	RRT: study: (21), Col: (35.5)	For study patients: 63, for Col-treated patients: 61	For Col-treated patients: median APACHE II score: 20 (range 8–45)
Zarkotou 2011	Greece/ 2008–2010	Prospective case–control	BSI (100)	KPC *K. pneumoniae* (100)	Overall: 53, Col-treated: 21 (7/14)	NR	Not applicable	Tig, Gen: active (10% and 4% of the isolates R, respectively), Mer: not active (60% of the isolates R)	NR	For study patients: 71.7	For study patients: mean APACHE II score at admission: 21, mean APACHE II score at infection onset: 21.1
Capone 2013	Italy/ 2010–2011	Prospective cohort	BSI, lower RTI, IAI, UTI , SSTI (percentages NR)	Carb-R *K. pneumoniae* (100)	Overall: 91[g], Col-treated: 48 (11/37)	NR	Not applicable	Tig, Col: active (20% and 36% of the isolates R, respectively), Gen, Fos: not active (80% and 50% of the isolates R, respectively)	CRF: study: (30)	For study patients: 48	For study patients: median APACHE II score: 15 (IQR 12–20)
Mouloudi 2010	Greece/ 2007–2008	Retrospective case–control	BSI (100)	Carb-S *K. pneumoniae* (37), MBL *K. pneumoniae* (31), KPC *K. pneumoniae* (32)	Overall: 59, Col-treated: 53 (35/18)	NR	Not applicable	Col: active (all isolates S), Gen: active (11% of MBL- and KPC-producing strains R)	Renal disease: study: (19)	100	For study patients: median APACHE II score on ICU admission: 21 (range 4–37)

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Table 1
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Author/year of publication (reference)	Region/ study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of study or Col-treated patients (Col mono/Col combo)	Mean/median IV Col dose (MIU/24 h)[a,b]	Ratio of mean/ median Col dose to highest dose[c]	Activity of antibiotic combination[d]	Renal impairment (baseline) (% of study or Col-treated population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Souli 2008	Greece/ 2003–2006	Retrospective cohort	BSI (57), CR-BSI (29), VAP (21)[h]	MBL *K. pneumoniae* (79), MBL *K. oxytoca* (7), MBL *E. cloacae* (7), MBL *E. aerogenes* (7)	Overall: 16, Col-treated: 14 (2/12)	9[k]	1	Tzp, Caz: not active (all isolates R), Cipro, Imi, Mer: not active (88%, 53% and 47% of the isolates R, respectively), Gen, Amk: active (12% and 18% of the isolates R, respectively)	For Col-treated patients: ARF: (28.5), ARF (CVVH): (21), CRF: (14), for study patients: CRF (CVVH): (6)	For study patients: 62.5, for Col-treated patients: 57	For study patients: median APACHE II score on first day of infection: 22 (range 10–33)
Tumbarello 2012	Italy/ 2010–2011	Retrospective cohort	BSI (100)	KPC *K. pneumoniae* (100)	Overall: 125, Col-treated: 73 (22/51)	6–9[k]	0.66–1	Mer: not active (89% R) Col, Tig, Gen: active (12%, 9% and 6% R, respectively)	CRF: study: (10)	For study patients: 42	For study patients: mean APACHE II score: survivors: 24 (±15), non-survivors: 40 (±22)
Porwal 2014	India/ 2011–2012	Retrospective cohort	BSI (100)	Carb-R bacteria (100): *K. pneumoniae* (44), *E. coli* (26), *A. baumannii* (20), *P. aeruginosa* (10)	50 (41 of them continued or completed treatment) (12/29)	Mean: 5.18	0.57	NR	CRF (27)	100	Mean APACHE II score at onset of infection: 19.64 (±3.8)
Kontopidou 2014	Greece/ 2009–2010	Half-retrospective, half-prospective	CR-BSI (30.7), VAP (27.6), BSI (23.6), UTI (10.2), IAI (4.7), SSTI (3.1)	Carb-R *K. pneumoniae* (100)	Overall: 127, Col-treated: 57 (26–31)	9[l]	1	Amk, Mer: not active (64% and 98% R, respectively), Col, Tig, Gen: active (20%, 33% and 21% R, respectively)	CRF: study: (13)	For study patients: 100	For study patients: mean APACHE II score at admission: 18.2 (range 0–40)
Daikos 2014	Greece/ 2009–2010	Retrospective cohort	BSI (100)	Carb-R KPC, VIM *K. pneumoniae* (100)	Overall: 205, Col-treated: 61 (22/39)	9[k]	1	Imi, Mer, Dor, Amk: not active (53%, 54%, 57% and 68% R, respectively), Tig, Col, Gen: active (15%, 25% and 31% R, respectively)	NR	For study patients: 56.6	NR
Pintado 2008	Spain/ 1995–2006	Retrospective cohort	Pneumonia (60), IAI (10), UTI (8.3), SSI (6.6), BSI (5), other (9.8)	MDR Gram-negative bacteria (100): *Acinetobacter* spp. (50), *P. aeruginosa* (23.3), *K. pneumoniae* (13.3), *Enterobacter* spp. (10), *S. maltophilia* (1.6), *E. coli* (1.6)	60 (8/52)	Mean: Col mono: 3.29, Col combo: 3.95[b,e]	Col mono: 0.36, Col combo: 0.43	Pip, Caz, Imi, Cipro: not active	CRF (1.7)	68	Mean APACHE II score: 11.2 (±7.7) (range 3–37)
Garnacho-Montero 2013	Spain/ 2008–2011	Retrospective cohort	VAP (86), BSI (14)	Carb-R *A. baumannii* (100)	57 (28/29)	Mean: Col mono: 7, Col combo: 6.5	Col mono: 0.77, Col combo: 0.72	NR	CRF (5.3)	100	Mean APACHE II score: Col mono: 19 (±6.4), Col combo: 16 (±6)
Yilmaz 2015	Turkey/ 2011–2013	Retrospective cohort	VAP (100)	MDR *A. baumannii* (58.6) XDR *A. baumannii* (41.4)	70 (17/53)	6.75–9[f,k]	0.75–1	Imi, Mer: not active (100% R), Sulb: not active (93% R)	ARF (8.6), CRF (17.1)	100	NR

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Table 1
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Author/year of publication (reference)	Region/ study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of study or Col-treated patients (Col mono/Col combo)	Mean/median IV Col dose (MIU/24 h)[a,b]	Ratio of mean/ median Col dose to highest dose[c]	Activity of antibiotic combination[d]	Renal impairment (baseline) (% of study or Col-treated population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Petrosillo 2014	Italy, Croatia, Turkey/ 2010–2011	Retrospective cohort	VAP (64.5), BSI (19.9), SSI (3.6), UTI (3), IAI (2.4)[i]	MDR *A. baumannii* (59.6), *P. aeruginosa* (18.7), Carb-R *K. pneumoniae* (14.5), non-MDR *A. baumannii* (7.8), non-MDR *P. aeruginosa* (3), ESBL *E. coli* (0.6), *M. morganii* (0.6)[j]	166 (61/105)	Median: 6	0.66	Carb: not active (56.3% R)	Renal disease (25.3)	100	For Col-treated patients: median APACHE II score: 20 (IQR 17–24), median APACHE II score on ICU admission: Col mono: 20 (IQR 18–23), Col combo: 21 (IQR 14–26.5)
Parchem 2016	USA/ 2006–2012	Retrospective cohort	Pneumonia (100)	MDR *Acinetobacter* spp. (82.2), *P. aeruginosa* (20), *K. pneumoniae* (1.1)[j]	90 (49/41)	Median: Col mono: 4.14, Col combo: 4.32	Col mono: 0.46, Col combo: 0.48	Tig, Min, A–S, Imi–cil, Dor, AG, Cfpm, Tzp: active (combination therapy: administration of additional antibiotic to Col to which the MDR organism was I/S)	Renal impairment (percentage NR)	100	Median APACHE II score: Col mono: 24 (IQR 18–28), Col combo: 25 (IQR 19–31)
Falagas 2008	Greece 2006–2007	Retrospective case series	For Col-treated patients: RTI (25), BSI (20), SSI (20), CR-BSI (20), other (15)	For Col-treated patients: PDR Gram-negative bacteria (100): *K. pneumoniae* (80), *A. baumannii* (10), *P. aeruginosa* (10)	Overall: 24, Col-treated: 20 (4/16)[g]	NR	Not applicable	Mer, Cipro, Tzp, Trim–sulf, Gen, Chlor, Rif, A–S, Azt: not active (PDR Gram-negative bacteria)	ARF: Col: (10)	100	NR
López-Cortés 2014	Spain/ 2010	Prospective cohort	For study patients: VAP (34.7), pneumonia (15.8), SSTI (12.9), tracheobronchitis (9.9), UTI (9.9), IAI (7.9), other (8.9)	MDR *A. baumannii* (100)	Overall: 101, Col-treated: 73 (46/23)	6–9[k]	0.66–1	Carb: not active (64% of the isolates R)	ESRD: study: (3)	For study patients: 62.4	NR
Daikos 2009	Greece/ 2004–2006	Prospective cohort	BSI (100)	*K. pneumoniae* VIM-1-negative (58.6),VIM-1-positive (41.4)	Overall: 162, 67 patients with VIM-1-positive *K. pneumoniae*, 23 of them treated with Col (Col mono: 15, Col combo: 8)	NR	Not applicable	Carb: active (8.6% of the isolates R)	NR	For study patients: 32.7	NR
Hernández-Torres 2011	Spain/ 2007–2008	Prospective cohort	BSI (35) non-BSI (65)	MDR and Carb-R *A. baumannii* (100)	Overall: 77, Col-treated: 24 (4/20)[g]	NR	Not applicable	Col: active (all isolates S), Tig: active (30% of the isolates R)	For study patients: RF (14)	For study patients: 83	NR

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Table 1
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Author/year of publication (reference)	Region/ study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of study or Col-treated patients (Col mono/Col combo)	Mean/median IV Col dose (MIU/24 h)[a,b]	Ratio of mean/ median Col dose to highest dose[c]	Activity of antibiotic combination[d]	Renal impairment (baseline) (% of study or Col-treated population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Özvatan 2015	Turkey/ 1996–2010	Retrospective cohort	HAP (100, 95% of them VAP)	*Acinetobacter* spp. (100)	Overall: 356, Col-treated: 95 (6/89)	3–6[k]	0.33–0.66	NR	For study patients: CRF (2.8)	NR	For study patients: median APACHE II score at 14 days: survivors: 20 (range 3–38), non-survivors: 24 (range 8–37), median APACHE II score at 30 days: survivors: 19 (range 3–31), non-survivors: 23 (range 8–37)
Vardakas 2014	Greece/ 2006–2009	Retrospective cohort	For study patients: pBSI (33.7), sBSI (28.8), non-BSI (37.5)	*K. pneumoniae* (100, 76.9% Carb-R)	Overall: 104, Col-treated: 52 (15/37)	NR	Not applicable	Carb, Amk: not active (76.9% and 45.2% of the isolates R, respectively), Tig, Gen, Col: active (3.8%, 15.8% and 32.6% of the isolates R, respectively)	For study patients: ARF (20.2), CRF (15.4)	100	For study patients: mean APACHE II score: 17.9 (±6.9)
Samonis 2014	Greece/ 2004–2010	Retrospective cohort	For study patients: BSI (54), UTI (19), pneumonia (14), SSTI (12), other (1)	*P. aeruginosa* (100, 23% XDR)	Overall: 89, Col-treated: 15 (8/7)	NR	Not applicable	NR	For study patients: chronic renal disease (12.4)	For study patients: 5.15	NR
Papadimitriou-Olivgeris 2014	Greece/ NR	Retrospective cohort	For study patients: pBSI (60.4), CR-BSI (30.2), sBSI (9.4)	KPC *K. pneumoniae* (100, 24.5% PDR)	Overall: 53, Col-treated: 26 (available data for 19: Col mono: 2, Col combo: 17)[g]	NR	Not applicable	Col: not active (54.7% R), Gen: not active (52.8% R), Tig: active (34% R)	For study patients: CRF (5.7)	100	For study patients: mean APACHE II score on admission: 16.1 +– 7.9
Navarro-San Francisco 2012	Spain/ 2010–2012	Prospective cohort	For Col-treated patients: pBSI (22.2), sBSI (77.8)	For Col-treated patients: *K. pneumoniae* (100)	Overall: 40, Col-treated: 18 (1/17)	NR	Not applicable	Fos: not active (47.5% R), Tig, Col, Amk: active (32.5%, 12.5% and 2.5% R, respectively)	NR	For study patients: 20	NR
Ku 2012	USA/ 2009	Retrospective cohort	For 80/90 Col-treated patients: pneumonia (48.9) SSTI (17.8) UTI (14.4) CR-BSI (7.8)	For Col-treated patients: *A. baumannii* (80), carb-R Enterobacteriaceae (8.9), co-infection (11.1)	Overall: 106, Col-treated: 90 (71/19)	NR	Not applicable	Col: active (7% I/R), Tig: not active (82% I/R)	For Col-treated patients: CRF (33.3)	For Col-treated patients: 22.2	NR
Chuang 2014	Taiwan/ 2009–2010	Retrospective cohort	Pneumonia (100)	MDR *A.baumannii* (100)	Overall: 294, Col-treated: 119 (101/18)	Mean: 5.4[e]	0.6	Col: active (all isolates S)	Chronic renal disease: study: (20.1), Col: (23.5)	100	For Col-treated patients: mean APACHE II score: 22.8 (±9.3)

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Table 1
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Author/year of publication (reference)	Region/ study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of study or Col-treated patients (Col mono/Col combo)	Mean/median IV Col dose (MIU/24 h)[a,b]	Ratio of mean/ median Col dose to highest dose[c]	Activity of antibiotic combination[d]	Renal impairment (baseline) (% of study or Col-treated population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Sirijatuphat 2014	Thailand/ 2010–2011	RCT	Pneumonia (76.6), pBSI (5.35), UTI (5.35), SSTI (3.2), IAI (6.4), CNSI (1.0), other (2.1)	Carb-R *A. baumannii* (100)	94 (47/47)	Mean: Col mono: 7.2, Col combo: 7.92[e]	Col mono: 0.8, Col combo: 0.88	NR	CRF: Col mono: (31.9), Col combo: (14.9)	NR	Mean APACHE II score at diagnosis: Col mono: 21.9 (±7.9), Col combo: 23.0 (±6.4), median APACHE II score at diagnosis: Col mono: 22, Col combo: 24
Jang 2009	Korea/ 2006–2007	Retrospective cohort	VAP (100)	MDR *A. baumannii* (100)	41 (22/19)	NR	Not applicable	Cef–sulb, Trim–sulf: not active (92.9% of the isolates I/R), Col, Min: active (7% and 10.7% of the isolates I/R, respectively)	RF (24.4)	100	APACHE II score on ICU admission: Col mono: 26.7 (±6.7), Col combo: 24.9 (±5.9), APACHE II score on treatment: Col mono: 27.8 (±7.6), Col combo: 26.7 (±6.8)

A. baumannii, *Acinetobacter baumannii*; AG, aminoglycoside; Amk, amikacin; APACHE, Acute Physiology and Chronic Health Evaluation; ARF, acute renal failure; A–S, ampicillin–sulbactam; Azt, aztreonam; BSI, bloodstream

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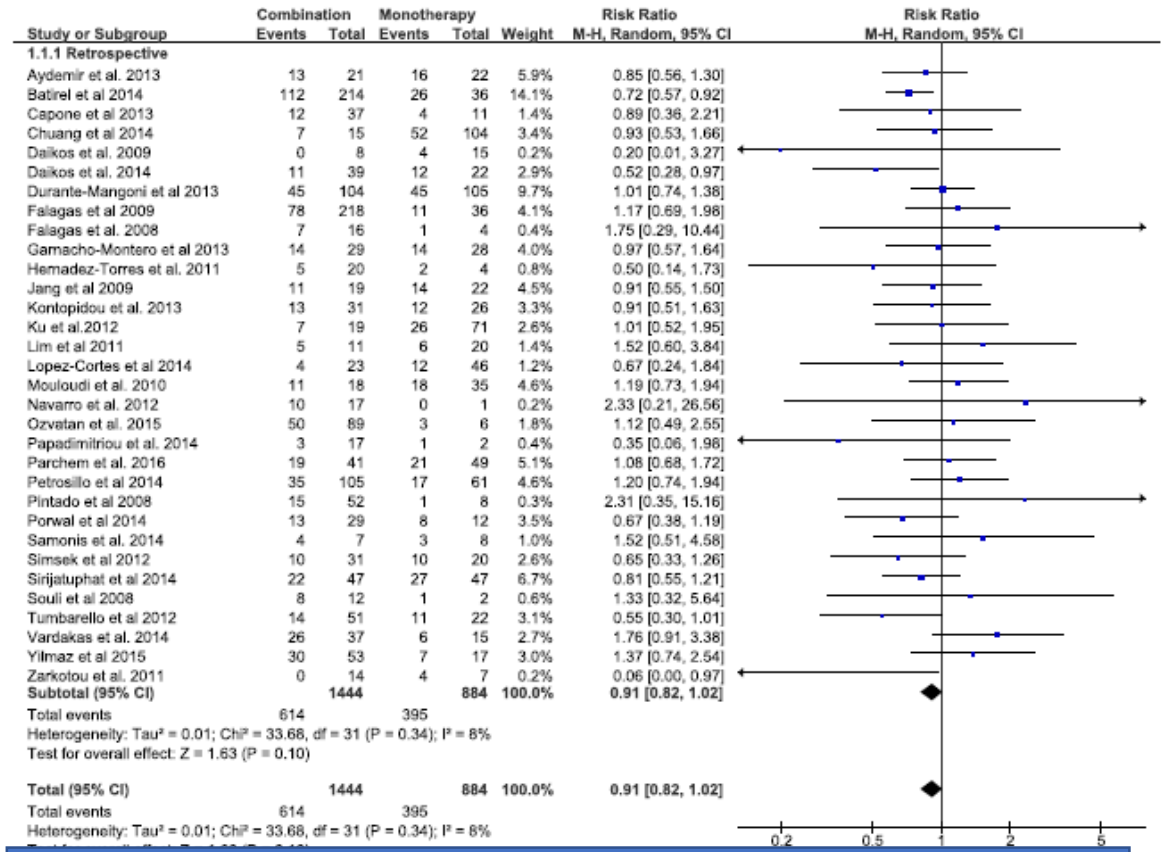

Fig. 2. Forest pl... ...olistin monotherapy. Vertical line, 'n... ...confidence intervals (CI). The area o... ...nszel.

Hiçbir alt grup analizinde fark saptanmamış

IV kolistinle yapılan kombinasyon tedavileri IV kolistin monoterapisine göre daha düşük mortaliteye sahip değil

IV kolistin monoterapisi de daha düşük mortaliteye sahip değil

IV kolistin kombinasyon tedavileri
- yüksek doz verildiği durumlarda,
- bakteremisi olan hastalarda,
- AB infeksiyonlarında ve
- Asya'da yapılan çalışmalarda daha anlamlı bulunmuş

Int J Antimicrob Agents 2018;51:535-547

Sonuç-yorum

- Daha önceki çalışmalarda kombinasyon tedavileri üstün bulunmuştu
  - Kombinasyonlar arasında farklılıklar var
- Bu çalışmada kombinasyon tedavileri ile kolistin monoterapisine üstün değil
  - Mortalitedeki relatif azalma düşük (<%10)

Int J Antimicrob Agents 2018;51:535-547

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

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- IV kolistinin akciğerlerde ulaştığı konsantrasyon tartışmalı
  - Yüksek doz verilirse de nefrotoksik ve nörotoksik
- Alternatif verilme yöntemlerinden birisi; inhale kullanım

- Rehberler inhale kullanım için ne diyor
  - ECCMID; önermiyor
  - IDSA; ancak duyarlı ise ve IV tedaviye yanıt alınamadıysa kullanılabilir diyor

- 13 çalışma değerlendirilmiş

J Infect 2018;76:321-7

Table 1
Characteristics of studies with comparison of intravenous colistin versus intravenous inhaled colistin.

Author/year of publication (reference)	Region/study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of patients (IV/IV-INH)	Mean/median IV/INH Col dose (MIU/24 h)[a,b]	Renal impairment (baseline) (% of total population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Demirdal 2016[6]	Turkey/2013–2014	Retrospective case-control	VAP (67.5) HAP (32.5)	*A. baumannnii* (100)	123 (80/43)	IV Col dose: 9[d,j] INH Col dose: 4.5[d]	CRF (6.5)	100	NR
Doshi 2013[12]	USA/2007–2009	Retrospective, cohort	Pneumonia (100)	MDR Gram-negative (100): *Acinetobacter* spp. (64) *Pseudomonas* spp. (56) ESBL *Klebsiella* spp. (12)[e]	95 (51/44)	Mean IV Col dose: IV group: 4.5 IV/INH group: 4.7[f] Median INH Col dose: 2.25[d]	CRF (18) ESRD (8.4)	100	Mean APACHE II IV: 24 (±6.9), IV/INH: 22.4 (±7.1)
Kofteridis 2010[7]	Greece/2005–2008	Retrospective case-control	VAP (100)	COS (100): *A. baumannii* (77) *K. pneumoniae* (14) *P. aeruginosa* (9)	86 (43/43)	IV Col dose: 9[j] INH Col dose: 2	RF (7)	100	Mean APACHE II IV: 17.7 (±7.6) IV/INH: 16.9 (±6.6)
Korbila 2010[16]	Greece/2005–2007	Retrospective cohort	VAP (100)	MDR Gram-negative (56% COS): *A. baumannii* (76) *P. aeruginosa* (18) *K. pneumoniae* (6)	121 (43/78)	Mean IV Col dose: IV group: 6.4 IV/INH group: 7.0 Mean INH Col dose: 2.1	CRF (8)	100	Mean APACHE II IV: 19.2 (±7), IV/INH: 17.4 (±6)
Naesens 2011[18]	Belgium/2007–2009	Retrospective cohort	VAP (30) HAP (70)	MDR *P. aeruginosa* (100, 50% COS)	20 (5/9), 6 patients only INH Col	IV Col dose: 4.5[b, g i] INH Col dose: 6	RRT (40)	100	Mean SOFA on admission: IV: 10 (range: 3–13), IV/INH: 6.4 (range: 0–15) at initiation of Col: IV: 6 (range: 3–9) IV/INH: 6.7 (range: 2–11)
Tumbarello 2013[20]	Italy/2005–2012	Retrospective cohort	VAP (100)	COS Gram-negative (100): *A. baumannii* (62) *P. aeruginosa* (25) *K. pneumoniae* (13)	208 (104/104)	Mean IV Col dose: IV group: 7.3 IV/INH group: 7 INH Col dose: 3	CRF (10), CRRT (20)	100	Median SOFA initiation of IV Col IV: 8 (IQR: 5–11) IV/INH: 7 (IQR: 6–12)
Ganapathy 2009[14]	United Kingdom/2003–2005	Retrospective cohort	Pneumonia (100)	MDR Acinetobacter spp./Pseudomonas spp. (100)	29 (6/17) 6 patients only INH Col	NR	CRF (percentage NR)	100	NR
Pérez-Pedrero 2010[19]	Spain/NR	Retrospective cohort	HAP (48) Tracheobronchitis (52)	MDR *A. baumannii* (100)	31 (14/10) 7 patients only INH Col[h]	NR	NR	100	Mean APACHE II IV: 12.8 (±5.7) IV/INH: 14.1 (±5.7)
Kalin 2012[15]	Turkey/2011	Retrospective cohort	VAP (100)	MDR *A. baumannii* (100)	45 (16/29)	IV Col dose: 9[f k] INH Col dose: 4.5[d]	CRF (4)	100	Median APACHE II 22

(*continued on next page*)

J Infect 2018;76:321-7

Table 1 (*continued*)

Author/year of publication (reference)	Region/study period	Study design	Infection (% of total population)	Bacterial species (%)	No. of patients (IV/IV-INH)	Mean/median IV/INH Col dose (MIU/24 h)[a,b]	Renal impairment (baseline) (% of total population)	ICU (% of total population)	Mean/median APACHE or SOFA score (±SD) (range) (IQR)
Falagas 2006[13]	Greece/2003–2005	Prospective case-series	VAP (33) UTI (26) SSI (15) Peritonitis (11) Other (15)	COS Gram-negative (100): *A. baumannii* (31.5) *P. aeruginosa* (45) *K. pneumoniae* (13) *E. coli* (10.5)	27 (18/9)	IV Col dose: 6[m] INH Col dose: 2	CRF (4), ESRD (7)	56	Mean APACHE II on ICU admission: 17.5 (range: 14–26) on treatment initiation: 14 (range: 9–25)
Korkmaz Ekren 2016[17]	Turkey/NR	Retrospective cohort	HAP (100)	MDR *A. baumannii* and *P. aeruginosa* (100)	279 (210/69)	Median IV Col dose: IV group: 9 IV/INH group: 6.75[d] INH Col dose: NR	NR	NR	Median APACHE II 22
Amin 2013[10]	Egypt/2011–2012	Prospective cohort	HAP (100)	COS Gram-negative (100): *A. baumannii* (65) *P. aeruginosa* (25) *K. pneumoniae* (10)	40 (12/28)	IV Col dose: 4.5[g,j] INH Col dose: 4	NR	100	Mean APACHE II IV: 19.1 (±7) IV/INH: 18.1 (±5)
Bogovič 2014[11]	Croatia/2013	Retrospective cohort	VAP (100)	MDR Gram-negative (100): *A. baumannii* (55) *P. aeruginosa* (84) *K. pneumoniae* (16)[e]	31 (23/8)	IV Col dose: 9 [l] INH Col dose: 4	RF (45)	100	NR

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation, COS colistin-only susceptible, CRF: chronic renal failure, CRRT: continuous renal replacement therapy, ESBL: extended-spectrum beta-lactamase, ESRD:

Verilerin kalitesi düşük-çok düşük olarak değerlendirilmiş

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Study or Subgroup	Inhaled/Intravenous Events	Total	Intravenous Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 inhaled						
Amin et al. 2013	8	28	5	12	2.6%	0.69 [0.28, 1.67]
Bogovic et al. 2014	6	8	17	23	8.4%	1.01 [0.64, 1.62]
Demirdal et al 2016	23	43	38	80	12.7%	1.13 [0.78, 1.62]
Doshi et al 2013	16	44	27	51	8.4%	0.69 [0.43, 1.10]
Falagas et al. 2006	2	9	2	18	0.7%	2.00 [0.33, 11.97]
Ganapathy et al 2009	10	17	2	6	1.5%	1.76 [0.53, 5.86]
Kalin et al. 2012	16	29	7	15	5.0%	1.18 [0.63, 2.23]
Kofteridis et al 2010	10	43	18	43	4.8%	0.56 [0.29, 1.06]
Korbila et al 2010	31	78	19	43	9.6%	0.90 [0.58, 1.39]
Korkmaz et al. 2016	45	69	128	210	26.2%	1.07 [0.87, 1.31]
Naesens et al 2011	3	9	5	5	2.7%	0.38 [0.16, 0.92]
Perez-Pedrero et al. 2010	2	10	5	14	1.1%	0.56 [0.13, 2.33]
Tumbarello et al. 2013	45	104	48	104	16.4%	0.94 [0.69, 1.27]
Subtotal (95% CI)		**491**		**624**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	217		321			
Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 12 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**491**		**624**	**100.0%**	**0.94 [0.81, 1.08]**
Total events	217		321			
Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 12 (P = 0.28); I² = 16%						
Test for overall effect: Z = 0.88 (P = 0.38)						
Test for subgroup differences: Not applicable						

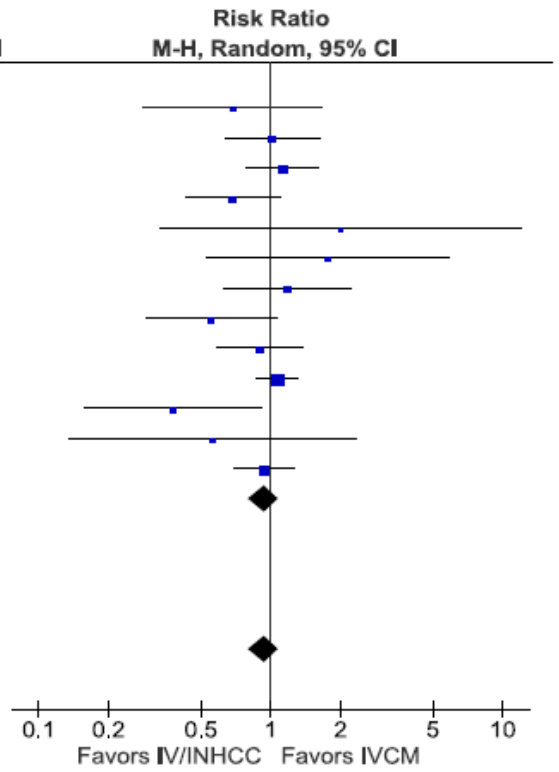

Fig. 2. Forest plot depicting the risk ratios (RR) of mortality among patients treated with IV/INHCC and IVCM. *(Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI. The areas of squares are proportional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

IV/INH kolistin kombinasyonu ile IV kolistin monoterapisi arasında fark bulunmamış

Alt grup analizinde düşük doz IV kolistin verilirse aradaki fark IV/INH kombinasyonu lehine oluyor

J Infect 2018;76:321-7

IV veya inhaler kolistin çalışmaları

- Bu meta-analizle benzer sonuçlar sağlamıştır
- Bir RKÇ'da inhale 4 MIU/gün ile tek veya kombine IV kolistin (9 MIU yükleme, sonra 2x4,5 MIU/gün) benzer etkinlik saptanmış
- Günümüzdeki bilgiler inhale antibiyotiklerin öneriler içerisinde yer alması için yeterli değil
- İyi düzenlenmiş RKÇ'lara ihtiyaç var

J Infect 2018;76:321-7

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

- Kolistin + meropenem kombinasyonu için ilk RKÇ

- Gruplar
  - IV kolistin monoterapi (n:198), (9 MIU yükleme, sonra 2x4,5 MIU/gün)
  - IV kol + meropenem (n:208) (2 gr uzamış infuzyon ile günde 3 kez)

Lancet Infect Dis 2018;18:391-400

Etkenler ve infeksiyon tipleri

	Colistin (n=198)	Colistin and meropenem (n=208)
Pathogen		
Acinetobacter baumannii	151 (76%)	161 (77%)
Enterobacteriacaeae	34 (17%)	39 (19%)
Pseudomonas/other	13 (7%)	8 (4%)
Type of infection		
Bacteraemia	76 (38%)	97 (47%)
Ventilator-associated or hospital-acquired pneumonia	97 (49%)	85 (41%)
Probable ventilator-associated pneumonia	11 (6%)	14 (7%)
Urinary tract infection	14 (7%)	12 (6%)

Lancet Infect Dis 2018;18:391-400

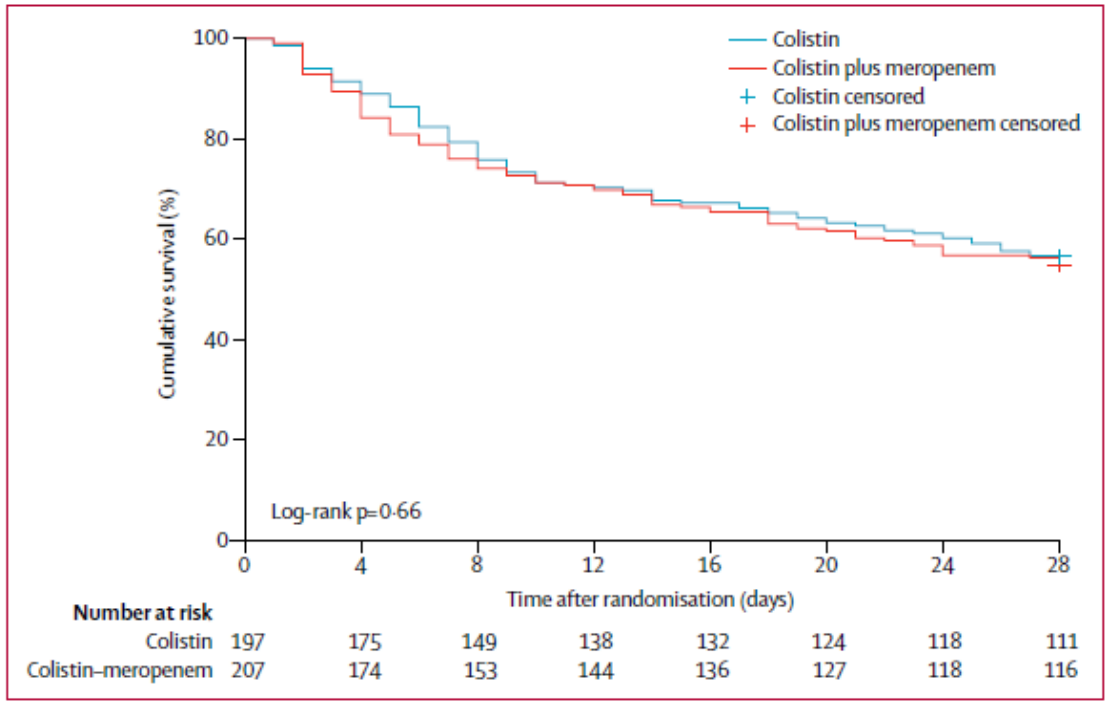

Figure 2: **Survival analysis to day 28 after randomisation**

Kolistin monoterapisi ile kolistin/meropenem kombinasyonu arasında 28 günlük sağkalım anlamında fark bulunmamıştır

Sonuçlar AB infeksiyonları için de aynı

Ciddi AB infeksiyonlarında meropenem katkısı ilave fayda sağlamıyor

Lancet Infect Dis 2018;18:391-400

	Colistin (n=198)	Colistin and meropenem (n=208)	RR (95% CI) for outcome with combination*	p value
Primary outcome				
Clinical failure at day 14	156 (79%)	152 (73%)	0·93 (0·83–1·03)	0·172
Secondary outcomes				
28-day mortality	86 (43%)	94 (45%)	1·03 (0·84–1·28)	0·781
Disposition at day 28	..	..	..	0·550
Dead	86 (43%)	94 (45%)	..	..
Alive, not discharged	60 (30%)	70 (34%)	..	..
Alive, discharged home	30 (15%)	22 (11%)	..	..
Alive, discharged to chronic care	22 (11%)	22 (11%)	..	..
14-day mortality	64 (32%)	70 (34%)	1·04 (0·79–1·37)	0·786
Failure with modification†	171 (86%)	177 (85%)	0·99 (0·91–1·07)	0·724
Microbiological failure	62 (31%)	73 (35%)	1·1 (0·84–1·44)	0·489
SOFA score day 7	5 (3–8), n=160	5 (3–8), n=162	..	0·643
SOFA score day 14	5 (3–7), n=126	4 (2–7), n=131	..	0·471
Febrile on day 3	62 (33%), n=186	71 (37%), n=194	1·11 (0·85–1·46)	0·444
Febrile on day 7	44 (27%), n=164	45 (26%), n=171	1·02 (0·71–1·45)	0·926
Time to defervescence, days	2 (0–6), n=191	2 (0–6), n=206	..	0·725
Time to weaning among ventilated patients, days	6 (0–22), n=110	4 (0–16), n=115	..	0·161
Time to intensive care unit discharge among patients discharged alive from intensive care unit, days	17 (8–28), n=52	22 (13–28), n=55	..	0·104
Time to discharge among patients discharged alive, days‡	15·0 (10·5–20·5), n=52	15·0 (11·0–20·0), n=44	..	0·635
Functional capacity independent, among 28-day survivors	12 (12%), n=101	8 (7%), n=108	0·60 (0·27–1·33)	0·209
Clinically significant superinfection by day 28	58 (29%)	56 (27%)	0·92 (0·67–1·26)	0·610
New carbapenem-resistant bacteria in clinical samples by day 28	10 (5%)	18 (9%)	1·73 (0·83–3·64)	0·146
Colistin-resistant bacteria in clinical samples by day 28	11 (6%)	10 (5%)	0·89 (0·41–1·94)	0·768

Data are n (%) or median (IQR). n values indicated for outcomes assessed only for survivors, or if patient data are missing. RR=risk ratio. SOFA=Sequential Organ Failure Assessment. *RRs stratified by centre, RR>1 more failures with combination therapy. RRs not assessed for continuous variables. †Composite failure at day 14 or any deviation from assigned regimen until day 10. ‡Up to 28 days.

Table 2: **Outcomes for intention-to-treat population**

Alt grup analizlerinde de meropenem ilavesinin ek bir katkısı yok

Etkene göre de fark yok

	Colistin	Colistin and meropenem	Risk ratio (95% CI) for outcome with combination	p value
Main pathogen				
n	198	208	..	..
Clinical failure				
Acinetobacter baumannii	125 (83%), n=151	130 (81%), n=161	0·97 (0·87–1·09)	0·643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0·78 (0·54–1·13)	0·185
Pseudomonas or others§	8 (62%), n=13	4 (50%), n=8	0·81 (0·36–1·84)	0·673
28-day mortality				
A baumannii	70 (46%), n=151	84 (52%), n=161	1·11 (0·87–1·41)	0·404
Enterobacteriaceae	12 (35%), n=34	8 (21%), n=39	0·62 (0·29–1·36)	0·235
Pseudomonas or others	4 (31), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0
14-day mortality				
A baumannii	54 (36%), n=151	62 (39%), n=161	1·11 (0·82–1·52)	0·495
Enterobacteriaceae	6 (18%), n=34	6 (15%), n=39	0·90 (0·32–2·51)	0·838
Pseudomonas or others	4 (31%), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0

Lancet Infect Dis 2018;18:391-400

β-Lactam plus aminoglycoside or fluoroquinolone combination versus β-lactam monotherapy for *Pseudomonas aeruginosa* infections: A meta-analysis

Konstantinos Z. Vardakas[a,b], Giannoula S. Tansarli[a], Ioannis A. Bliziotis[a,b], Matthew E. Falagas[a,b,c,*]

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- 19 çalışma, 8'i RKÇ
- Kombinasyon tedavisi alanlar ile beta-laktam monoterapisi alanlar arasında mortalite açısından fark yok
- Klinik kür kombinasyon tedavisi grubunda daha yüksek ancak istatistiksel anlamlı değil
  - En yüksek klinik kür empirik kombinasyon tedavisi grubunda
- Sonuç: *P.aeruginosa* için kombinasyon tedavisinin mortalite açısından faydası yok

Int J Antimicrob Agents 2013;41:301– 310

P.aeruginosa infeksiyonlarında kombinasyon tedavileri

- Günümüzdeki verilerle *P.aeruginosa* infeksiyonlarında kombinasyon tedavisini destekleyen yeterli kanıt yoktur
- En iyi MDR-PA tedavisi için uzlaşılmış bir tedavi yaklaşımı yoktur
- Yetersiz başlangıç tedavisi yüksek mortaliteyle birliktedir
  - O halde soru: kombinasyon monoterapiden daha mı iyidir?
  - Yapısal pulmoner hastalık, bronşiektazi, kistik fibrozis gibi hastalarda özellikle VİP gelişmiş ise ikili tedavi başlanabilir
  - MDR-KDİ'de monoterapi/kombinasyon fark yok

Int J Antimicrob Agents 2013;41:301– 310

P.aeruginosa infeksiyonlarında kombinasyon tedavileri

- Başlangıçta kombine başlanabilir
  - Antipseudomonal sefalosporin, karbapenem, kinolon veya β-laktam/β-laktamaz inhibitörleri ile
  - Duyarlılık sonuçlarına göre monoterapiye geçilebilir
  - Septik şokta olan veya ölüm riski yüksek hastalarda kombine tedaviye devam edilebilir
- Sadece kolistin duyarlı ise
  - Uygun doz
  - Uygun doz aralığı (örneğin uzun infüzyon)
  - Uygun sürede verilmesi de önemli

Kombinasyon tedavilerinde kullanılan anti-pseudomonal ilaçlar

- IV fosfomisin
  - Monoterapi olarak verildiğinde tedavi başarısızlığı veya relapslar ortaya çıkmış
  - Mevcut *in vitro* verilere göre karbapenem olması gereken bir partnerle kombinasyonu dirençten kaçmak için uygulanır
- Tigesiklin
  - *In vitro* AB etkinliği iyi
  - Ancak *P.aeruginosa* için etkinliği yeterli değil, bu nedenle kombinasyon kaçınılmaz
  - Kombinasyon tedavilerinin en büyük sorunu XDR etkenlerle oluşan VİP'te PK/PD dezavantajlara bağlı gelişen başarısızlık
  - *In vivo*?

Tigecycline treatment experience against multidrug-resistant *Acinetobacter baumannii* infections: a systematic review and meta-analysis

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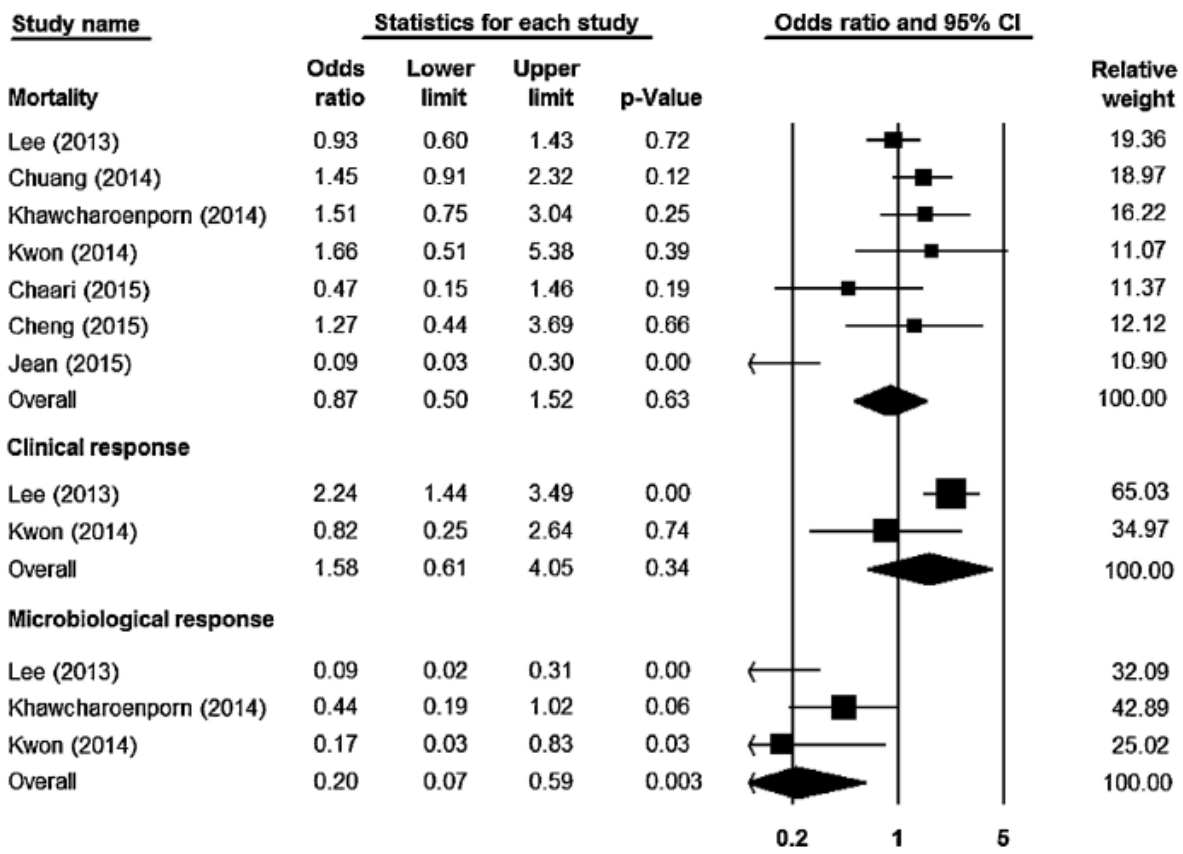


Tüm nedelere bağlı ölüm açısından tigesiklin ile kontrol grupları arasında fark yok

Int J Antimicrob Agents 2016;47:107-116

Subgrup analizinde mortalite kolistin bazlı tedavilere göre tigesiklin grubunda daha yüksek

Table 2
Subgroup analysis of mortality with tigecycline versus other antibiotics for the treatment of multidrug-resistant *Acinetobacter baumannii* infections in controlled studies.

Variable	No. of studies (no. of patients)	Mortality type	Mortality of tigecycline compared with controls [OR (95% CI); *P*-value]	Heterogeneity of studies included
By control group				
Tigecycline vs. colistin	3 (404)	In-hospital	1.57 (1.04–2.35); $P=0.03^{*}$	$I^2=0\%$; $Q=0.49$; $P=0.78$
Tigecycline vs. colistin	3 (300)	Monthly	1.13 (0.67–1.91); $P=0.64$	$I^2=33.21\%$; $Q=2.99$; $P=0.22$
Tigecycline vs. imipenem/sulbactam	2 (470)	Monthly	0.31 (0.03–2.98); $P=0.31$	$I^2=92.11\%$; $Q=12.67$; $P<0.001$
By infection (tigecycline vs. control)				
Prospective	2 (139)	Monthly	0.35 (0.03–4.54); $P=0.42$	$I^2=90.32\%$; $Q=10.33$; $P=0.001$

OR, odds ratio; CI, confidence interval.
* Statistically significant ($P<0.05$).

MDR-AB tedavisinde tigesiklin iyi bir seçenek değil, mortalite daha yüksek, mikrobiyolojik eradikasyon daha düşük ve hastanede kalış süresi daha uzun

Int J Antimicrob Agents 2016;47:107-116

- Rifampisin ve glikopeptidler
  - Rifampisin/kolistin kombinasyonu AB için *in vitro* neredeyse %100 sinerjistik sonuçlanıyor
    - Ancak *in vivo* deneyimleri başarılı değil
  - Kolistin + glikopeptid kombinasyonu kolistin dirençli AB için *in vitro* sinergistik
    - *In vivo* rolleri ise hala net değil
- Aminoglikozidler
  - Hızlı bakterisidal
  - Konsantrasyona bağlı öldürme, uzamış post-antibiyotik etki
  - Kritik hastalarda amikasin ve gentamisin değişken ve sub-terapotik konsantrasyonlarda kalabiliyor

Yeni ilaçlar

- Seftolozan/tazobaktam
  - Komplike intrabdominal ve USİ'de onaylı
  - Pnömoni ve KDİ çalışmaları devam ediyor
  - Gram negatif bakteriler, ESBL üreten Enterobactericeae, çok güçlü PA
    - MDR-PA'ya etkili, ancak karbapenemaz yapanlara değil

- Seftazidim/avibaktam
  - Benzer bakteriler ve endikasyonlar
    - Komplike intrabdominal ve USİ'de onaylı
  - Farkı anti-PA etkisi diğeri kadar güçlü değil
    - Metallo-beta-laktamazlara etkili değil
  - *K.pneumoniae*'nin karbapenemazlarına çok etkili

Yeni ilaçlar

- Imipenem/silastatin/relebaktam
  - Sınıf A ve C beta-laktamazlara etkili ancak metallo-beta-laktamazlara değil
  - MDR-PA, KPC üreten *K.pneumoniae ve* Enterobactericeae
  - Komplike intrabdominal, USİ ve pnömonide çalışmalar devam ediyor

Table 1. Novel β-lactamase inhibitors against carbapenem-resistant Enterobacteriaceae (CRE) and multidrug-resistant (MDR) Gram negative bacteria [4,14,15,21–23,26,30–32,63,65–66,75–76,78–79,92–95].

Antibiotic	Spectrum	Clinical Development program (since 2018)	Dosage
Ceftazidime-Avibactam	Activity against: Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and some class D enzymes (OXA-10, OXA-48) No active against MBL, Acinetobacter spp, and less activity against anaerobes	Approved in 2015 in U.S.A and in 2016 in Europe	CrCl >50: 2.5g q8h CrCl: 31–50: 1.25g q8h CrCl: 10–30: 0.94 g q12h CrCl <10: 0.94g q48h Hemodialysis:0.94 g q48h (administer after hemodialysis session) CVVH:1.25g q8h All doses administered over 2 hours
Meropenem-Vaborbactam	Activity against: Enterobacteriaceae producing ESBL, KPC, AmpC. No active against OXA-48-like, or MBL. As active as meropenem alone against *P. aeruginosa, Acinetobacter* spp., and *S. maltophilia*	Approved in 2017 in U.S.A	CrCl >50: 2g q8h CrCl: 30–49: 2g q8h CrCl: 15–29: 2g q12h CrCl <15: 1g q12h Hemodialysis: 1g q12h (administer after hemodialysis session) All doses administered over 3 hours
Aztreonam-Avibactam	Activity against: Enterobacteriaceae producing ESBL, KPC, AmpC, OXA-48 and MBL. As active as Aztreonam alone against *P. aeruginosa* and A. *baumannii*, including MBL-producing isolates	Phase 3	CrCl > 50: ATM 6g/AVI 2g CrCl: 31–50: ATM 3g/AVI 1 g CrCl:16–30: ATM 2025 mg/AVI 675 mg
Imipenem/cilastatin-Relebactam	Activity against: Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and porin mutations. Diminished inhibitor activity against OXA-48. No activity against MBL and *A. baumannii*	Phase 3	IMI-REL 200/100 mg to 500/250 mg, depending on renal function, q6h All doses administrated as a 30-minute infusion
Ceftaroline fosamil-Avibactam	Activity against: Enterobacteriaceae producing ESBL, KPC, Amp C and some class D enzymes (OXA-like). No activity against MBL. No activity against A. *baumannii* or *P. aeruginosa*.	Phase 2	CPT 600 mg/AVI 600 mg q8h or q12h is under investigation
Cefepime-Zidebactam	Activity against Enterobacteriaceae and *P. aeruginosa* producing ESBL, KPC, AmpC and MBL	Phase 2	N/A
Meropenem-Nacubactam	Activity against class A and class C β-lactamases	Phase 1	N/A

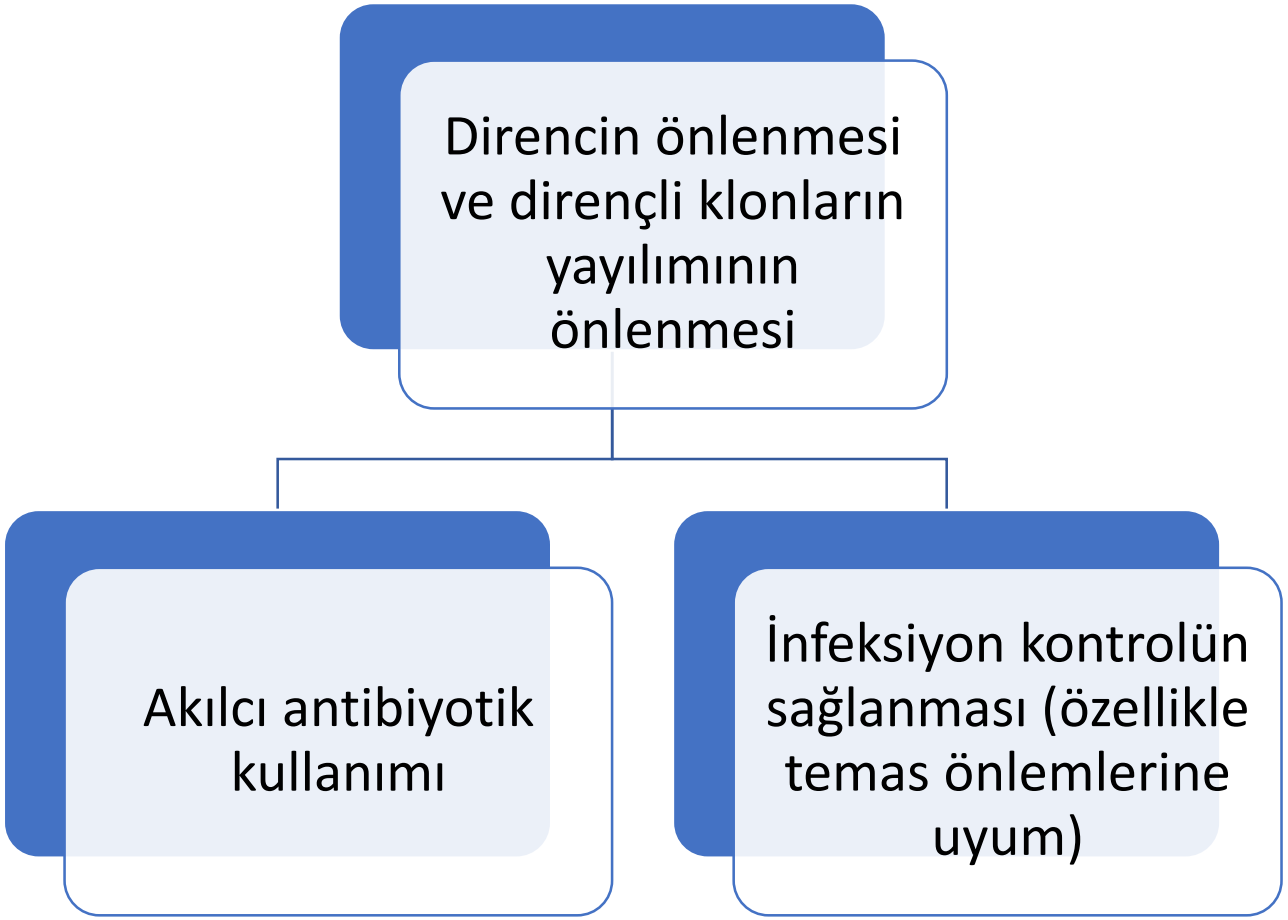
Yeni ilaçlar

- Karbapenemaz inhibitörleri
  - Avibaktam, relebaktam, vaborbaktam
- Umut vadeden aminoglikozidler
  - Plazomisin
- Siderofor sefalosporinler
  - Sefiderokol
    - XDR Enterobactericeae, XDR-AB ve CRPA'ya etkili en geniş spektrumlu
- Kurtarma tedavisi

A.baumanii infeksiyonlarında kombinasyon tedavileri

- Benzer şekilde RKÇ yok, dolayısıyla yeterli kanıt yok
- Bu nedenle kombine tedavinin monoterapiye üstünlüğünden bahsetmek zor
- Ancak immunsuprese hastalar, septik şok ve sınırda MIC'e sahip izolatlarla gelişen infeksiyonlarda kombinasyon tedavisi tavsiye edilebilir

Ne yapacağız?



Son söz

- Elimizdeki ilaçların (kolistin, tigesiklin, fosfomisin) azalan aktivitesi ve gelişen direnç günümüzde bizi kombinasyona itiyor
- Önümüzdeki 5 yıl içinde bu durum değişebilir
  - Yeni ilaçların gelmesiyle
    - Beta laktam/beta-laktamaz inhibitörleri, avibaktam, vaborbaktam, relebaktam içeren, plazomisin, sefiderokol, eravasiklin, murepavadin
  - Özel hasta gruplarında yapılacak randomize çalışmaların sonuçları
  - Moleküler tanı yöntemlerinin kullanımı da önem taşıyor
  - Faj tedavileri, anti-pseudomonal aşılar…