Gram-negatif Bakteri İnfeksiyonlarının Tedavisinde Yeni Antimikrobiyaller

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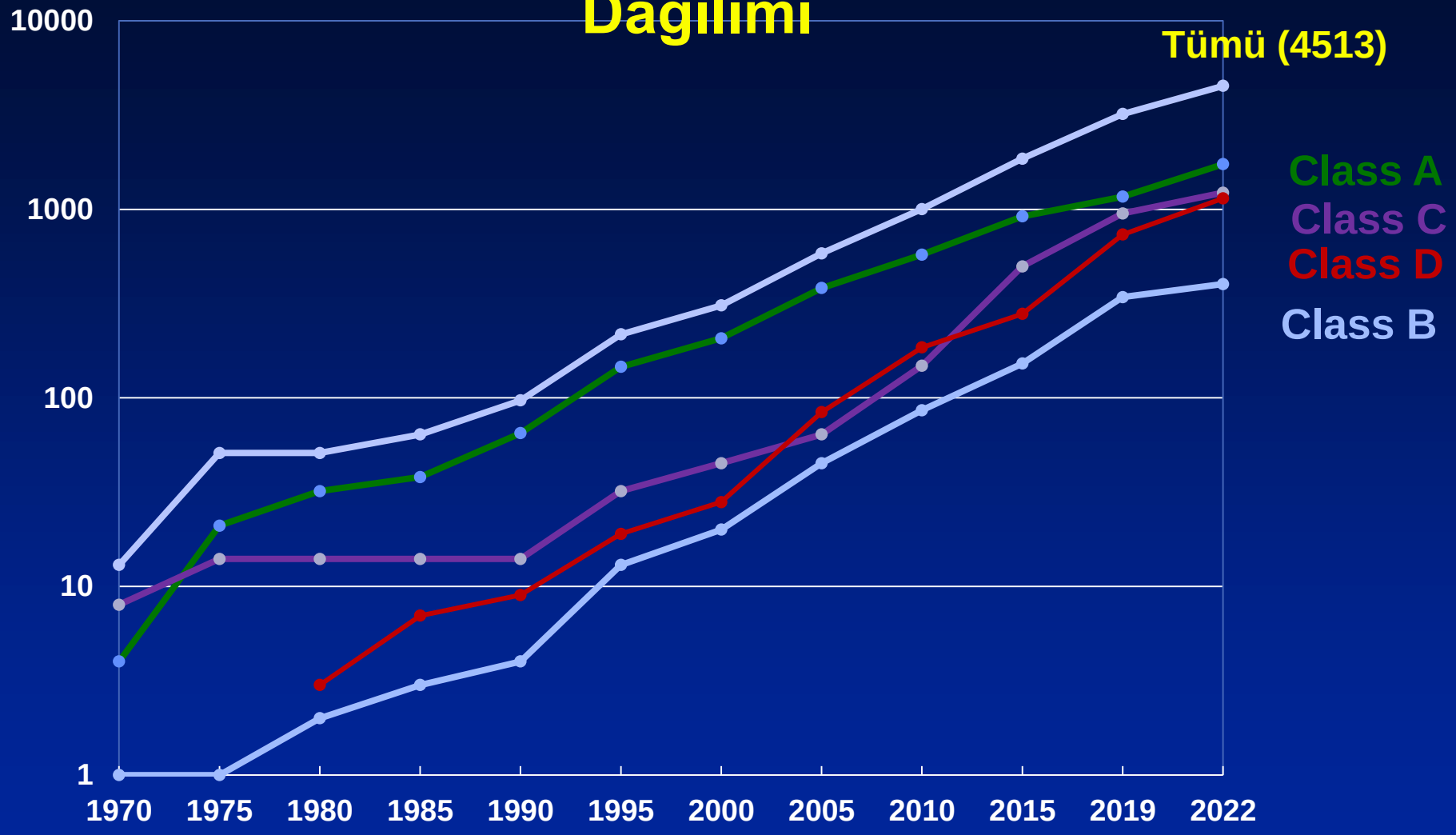
Hacettepe Üniversitesi Tıp Fakültesi
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD
Ankara

Beta-laktamazlar

Sınıf	Aktif bölge	Örnek enzimler
A	Serin	Hemen tüm plazmidik enzimler, *Klebsiellae kromozomal enzimi* *P. vulgaris*, *Bacteroides spp.*
B	Zn^{++}	*S. maltophilia* kromozomal L-1 *P. aeruginosa'da* plasmidik (IMP-1)
C	Serin	Kromozomal Amp C
D	Serin	*Enterobacterales*'te OXA enzimleri, plazmidik

Ambler, RP. 1980

Beta-laktamazların Yıllara Göre Dağılımı

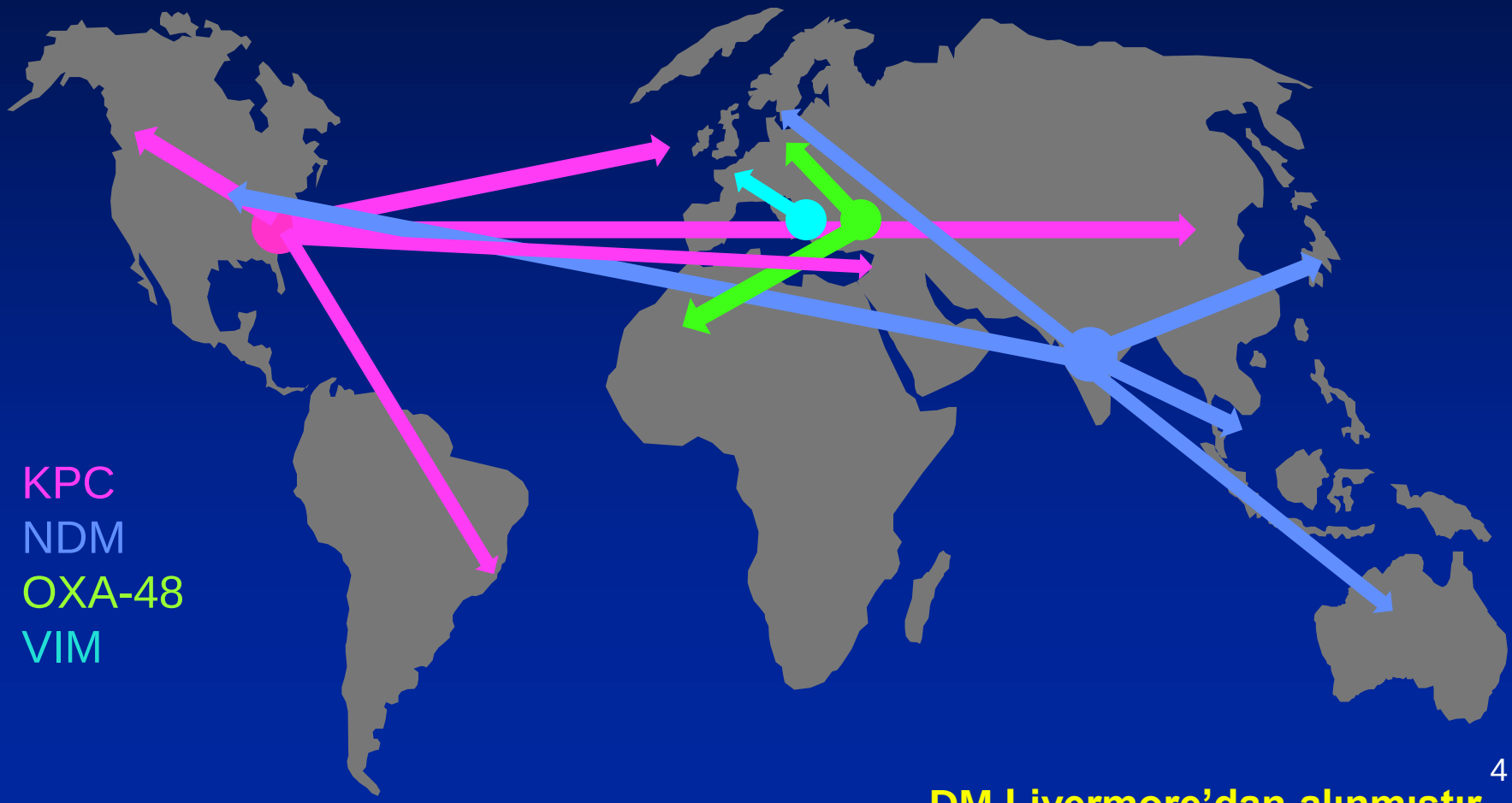


Bush K, personal communication

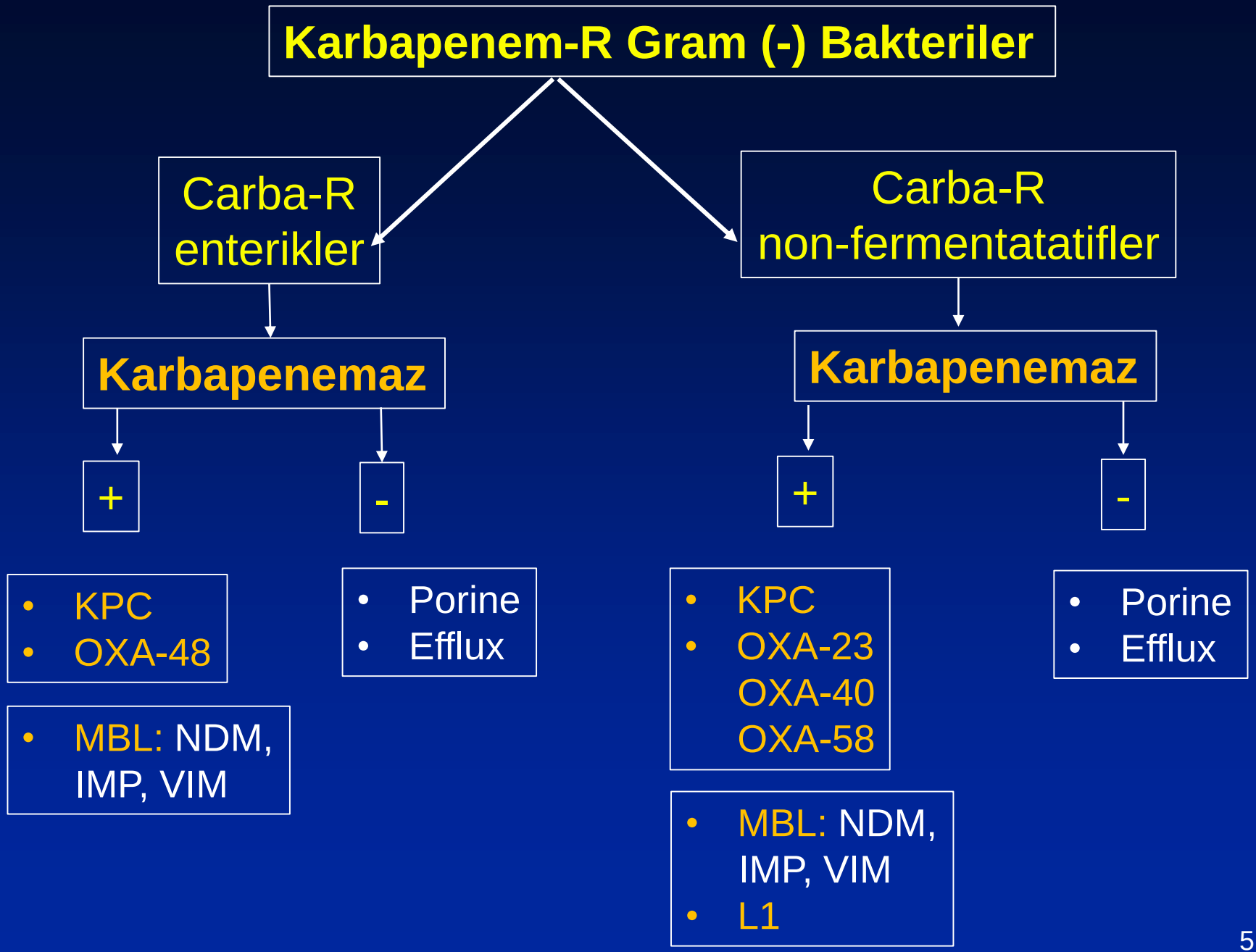
Data compiled from Bush, K. Antimicrob Agents Chemother 2018;62:e01076-18

http://www.lahey.org/Studies/ and https://www.ncbi.nlm.nih.gov/bioproject/PRJNA313047

Enterobacterales'te Karbapenemazlar

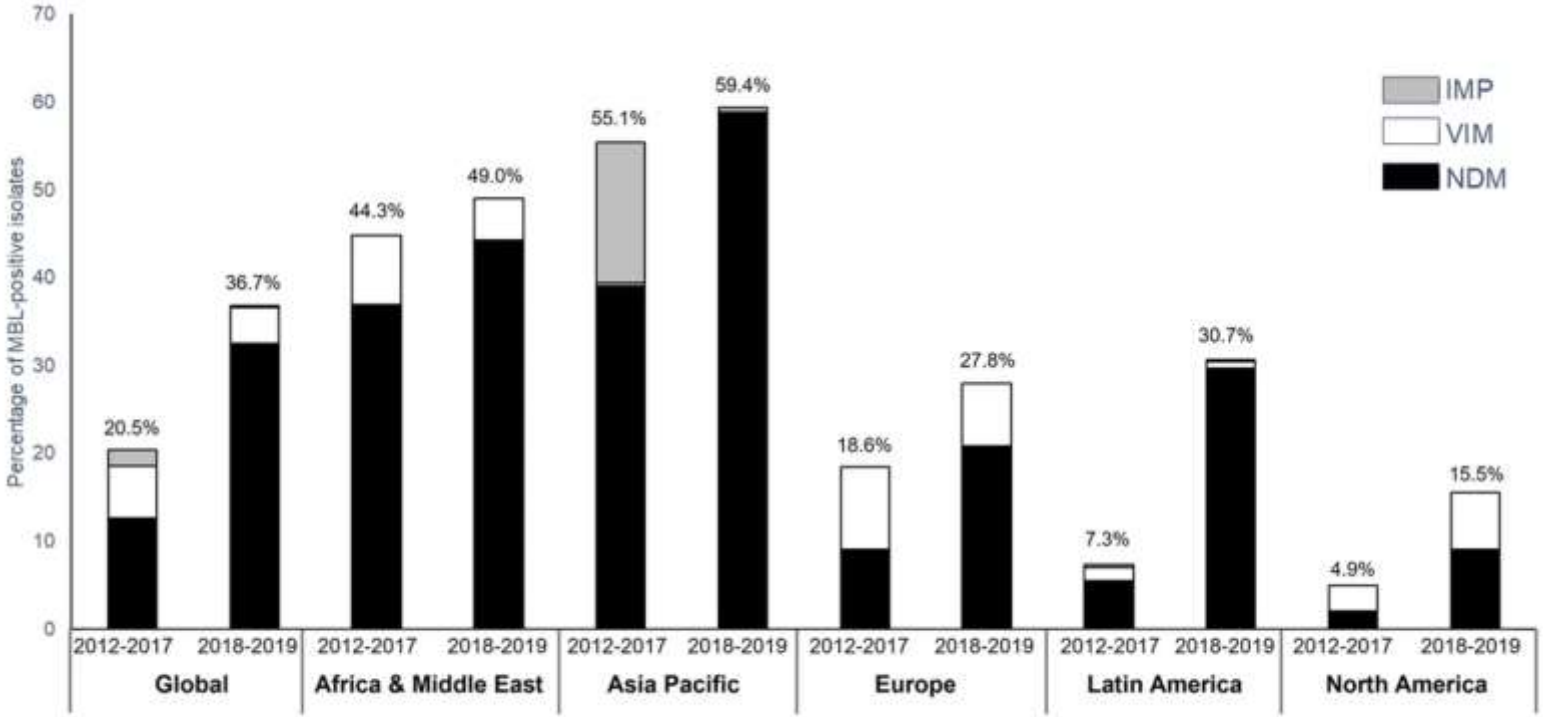


DM Livermore'dan alınmıştır



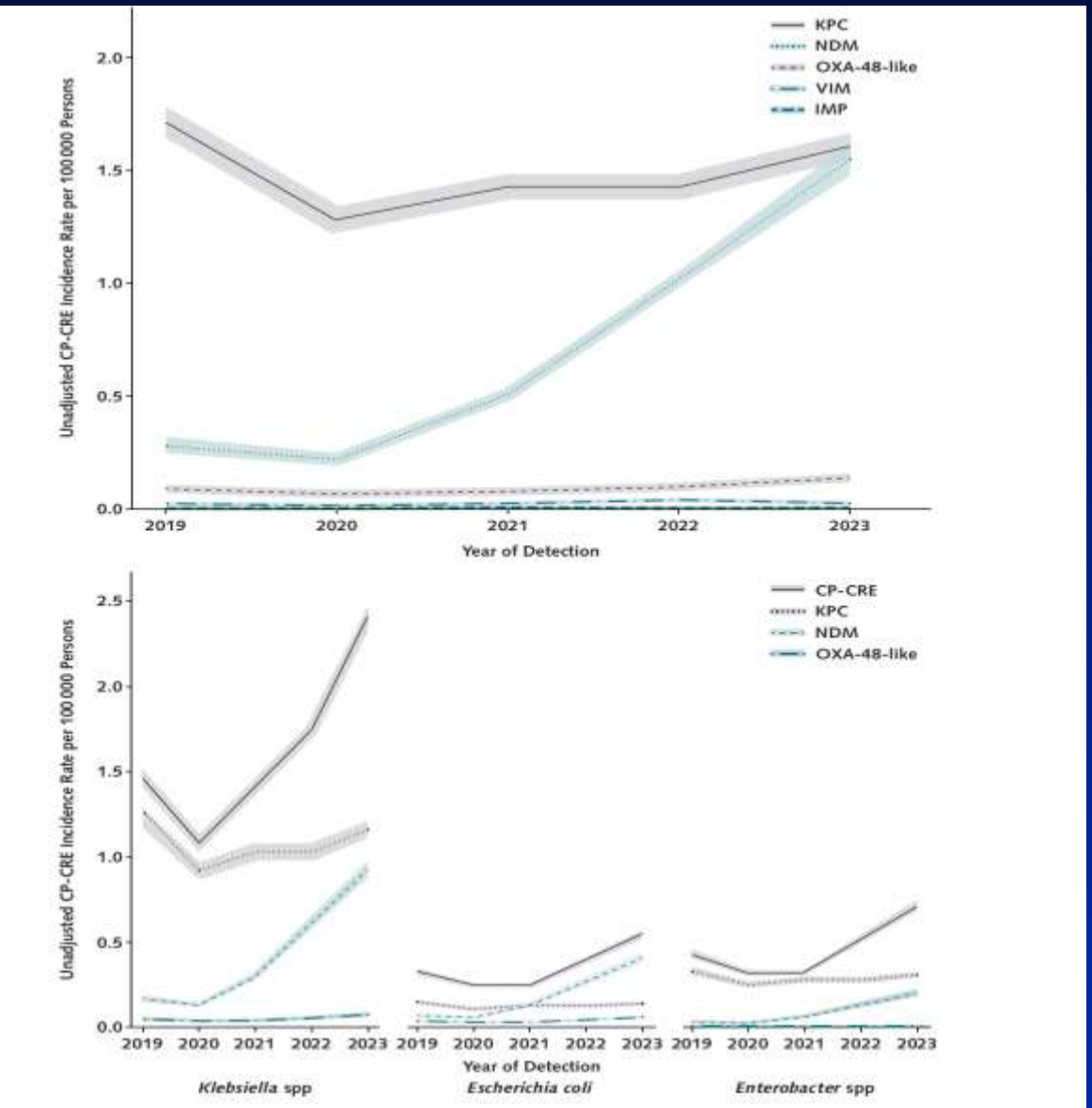
Nordmann P, Laurel P. Clin Infect Dis 2019;69 (suppl 7):S521

Karbapenem Dirençli *Enterobacterales* İzolatları İçinde of MBL (+) Suşların Dağılımı



Grabein B, et al. Infect Dis Ther 2024;13:2423

ABD'de Karbapenemazların Dağılımı 2019-2023



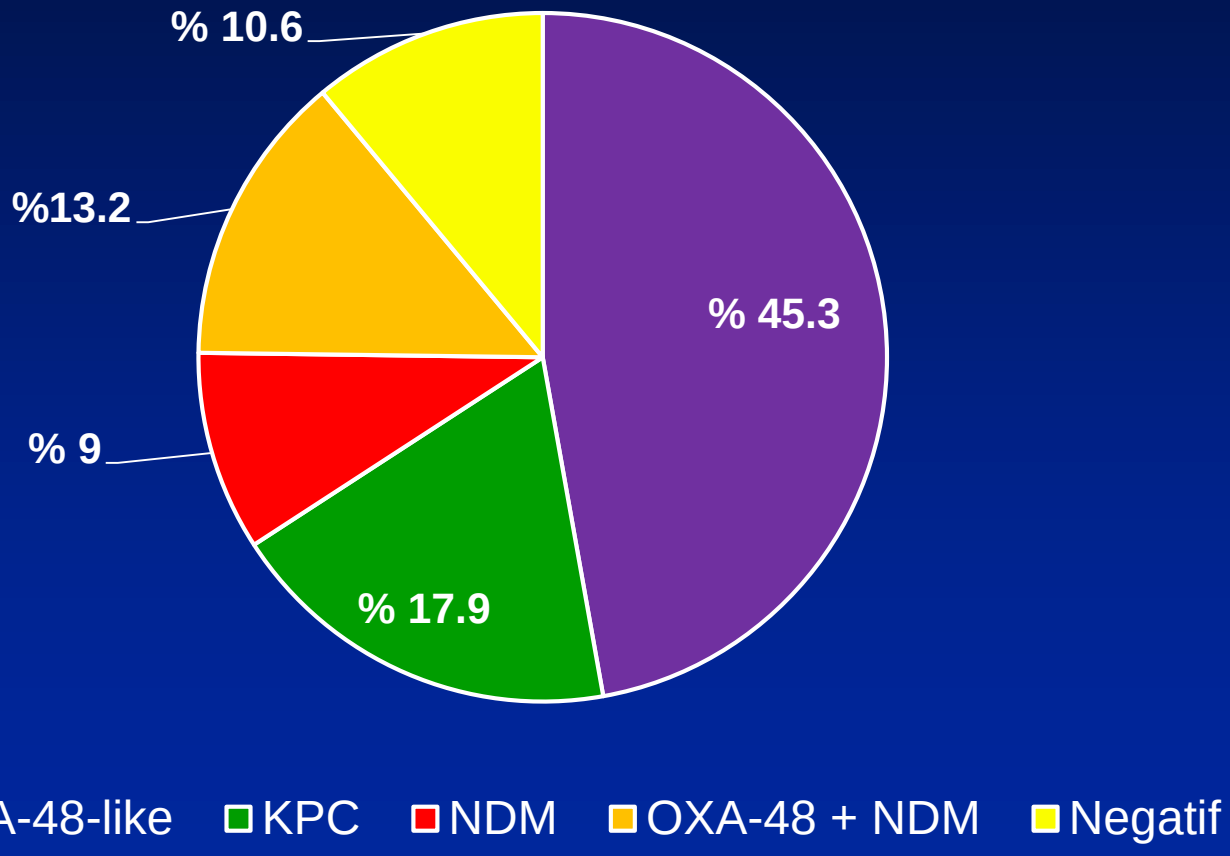
Rankin DA, et al. Ann Intern Med 2025; 78;1818

Clinical and Molecular Epidemiology of HospiTal-Acquired BloodstReam Infections caused by Gram-nEgative Bacteria in Türkiye: a Prospective Multi-center Cohort Study (TARGET study)

Abdullah T. Aslan[1,2*], Elif Seren Tanrıverdi[3], Osman Dağ[4], Cansu Çimen[5], Ayşe Kaya Kalem[6], Bircan Kayaaslan[6], Sevil Alkan[7], Bahadır Köylü[8], Emine Büşra Ata[8], Bilge Çağlar[9], Neşe Saltoğlu[9], Uğur Önal[10], Seçil Deniz[11], Onur Ural[12], Murtaza Öz[13], Mehmet Bakır[13], Mesut Yılmaz[14], Rümeysa Dinleyici[14], Ayşe Batırel[15], Özlem Akdoğan[16], Nurcan Baykam[16], Çiğdem Erol[17], Tuğba Yanık Yalçın[17], Oya Özlem Eren[18], Zeynep Türe Yüce[19], Gamze Kalın Ünüvar[19], Zuhal Özer Şimşek[20], Seda Güzeldağ[21], Adem Köse[22], Mustafa Cihangiroğlu[23], Dilek Yağcı[24], Muhammed Burak Sevinç[25], Zerrin Aktaş[26], Mustafa Oral Öncül[25], Gülden Ersöz[27], Ayşe Sesin Kocagöz[28], Gülşen Hazırolan[29], Tuğçe Ünalan-Altıntop[30], Bedia Dinç[31], Nazmiye Ülkü Tüzemen[32], Alper Akçalı[33], Salih Maçin[34], Ahmet Çalışkan[35], Mürşit Hasbek[36], Cem Ergon[37], Yasemin Ay Altıntop[38], Müge Şimşek[39], Barış Otlu[3], Kay A. Ramsay[1], Brian Forde[40], Budi Permada[40], Patrick N.A. Harris[1], Murat Akova[41], David L. Paterson[42], on behalf of the Study Group for Carbapenem Resistance (SCARE)**

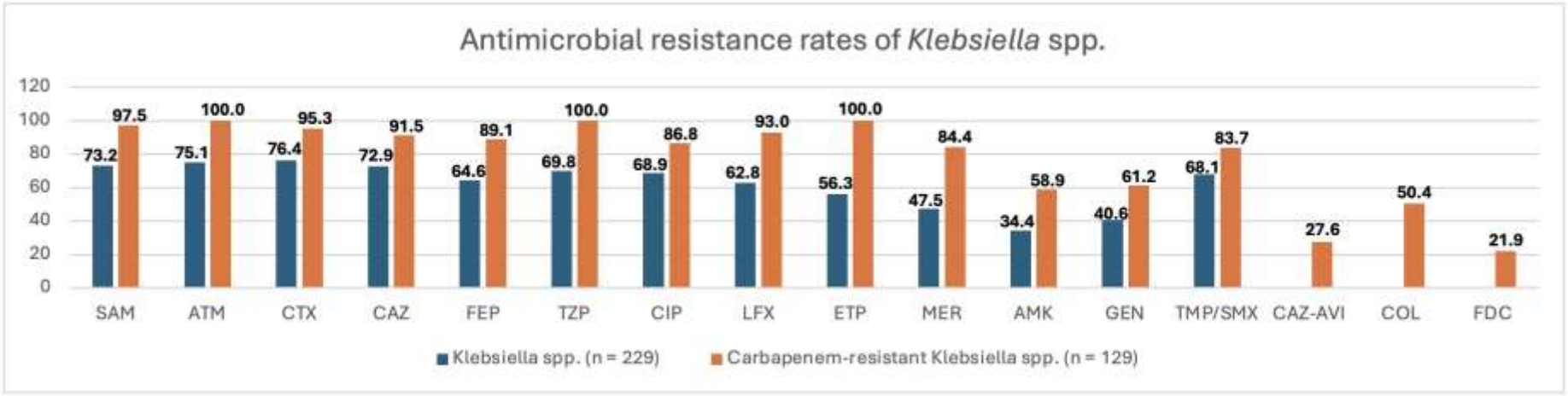
- **22 merkez, 680 bakteremik hasta, 2021-22**
  - **341 (% 50.1) karbapenem-R**
  - **339 (% 49.9) karbapenem-S**
  - **% 33.7 *Klebsiella spp*., % 21.9 *E. coli***
  - **% 21 *Acinetobacter spp.***

K. pneumoniae'de Karbapenemaz Dağılımı

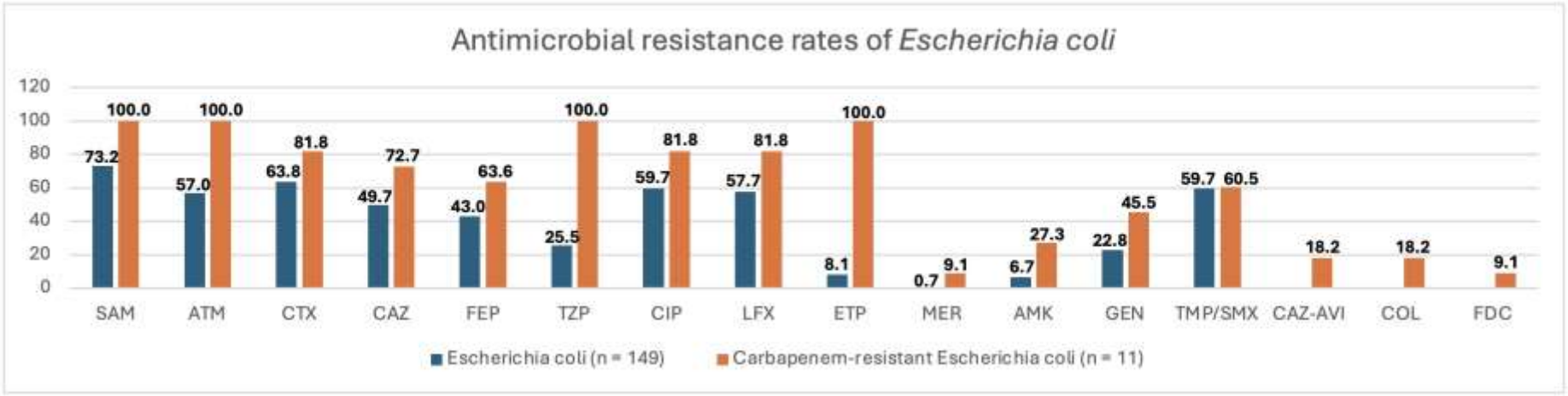


Aslan AT ve ark. Yayınlanmamış veri

A



B



Aslan AT ve ark. Yayınlanmamış veri

#00868

Evolving epidemiology of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: Emergence of metallobetalactamases in an OXA-48-like endemic country and the susceptibilities to new antimicrobials

03. Bacterial susceptibility & resistance

03b. Resistance surveillance & epidemiology: Healthcare-associated bacteria

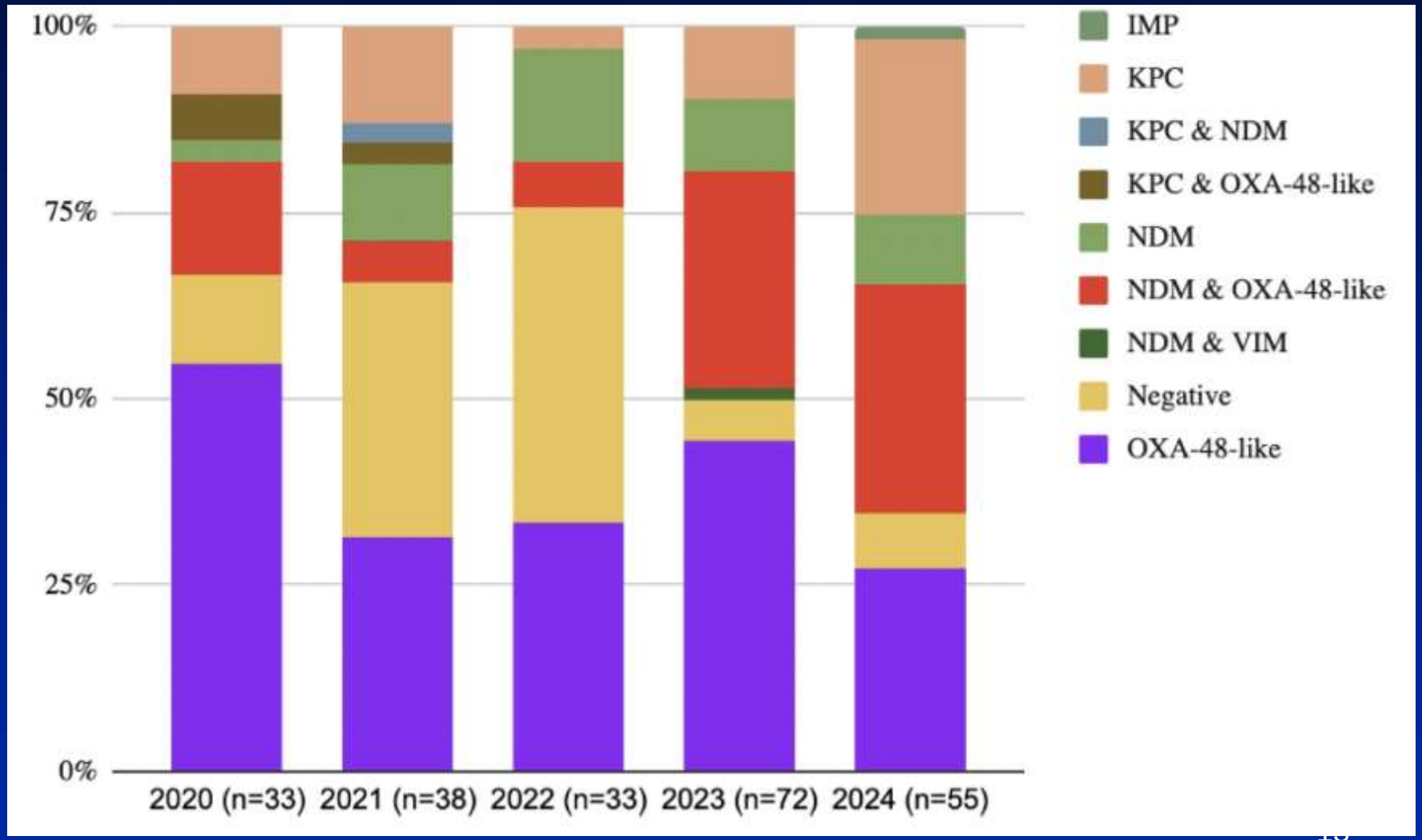
Are there any research groups, study groups or consortia to acknowledge? (Do not indicate funding sources or company support) Please do not exceed 100 characters limit.

No

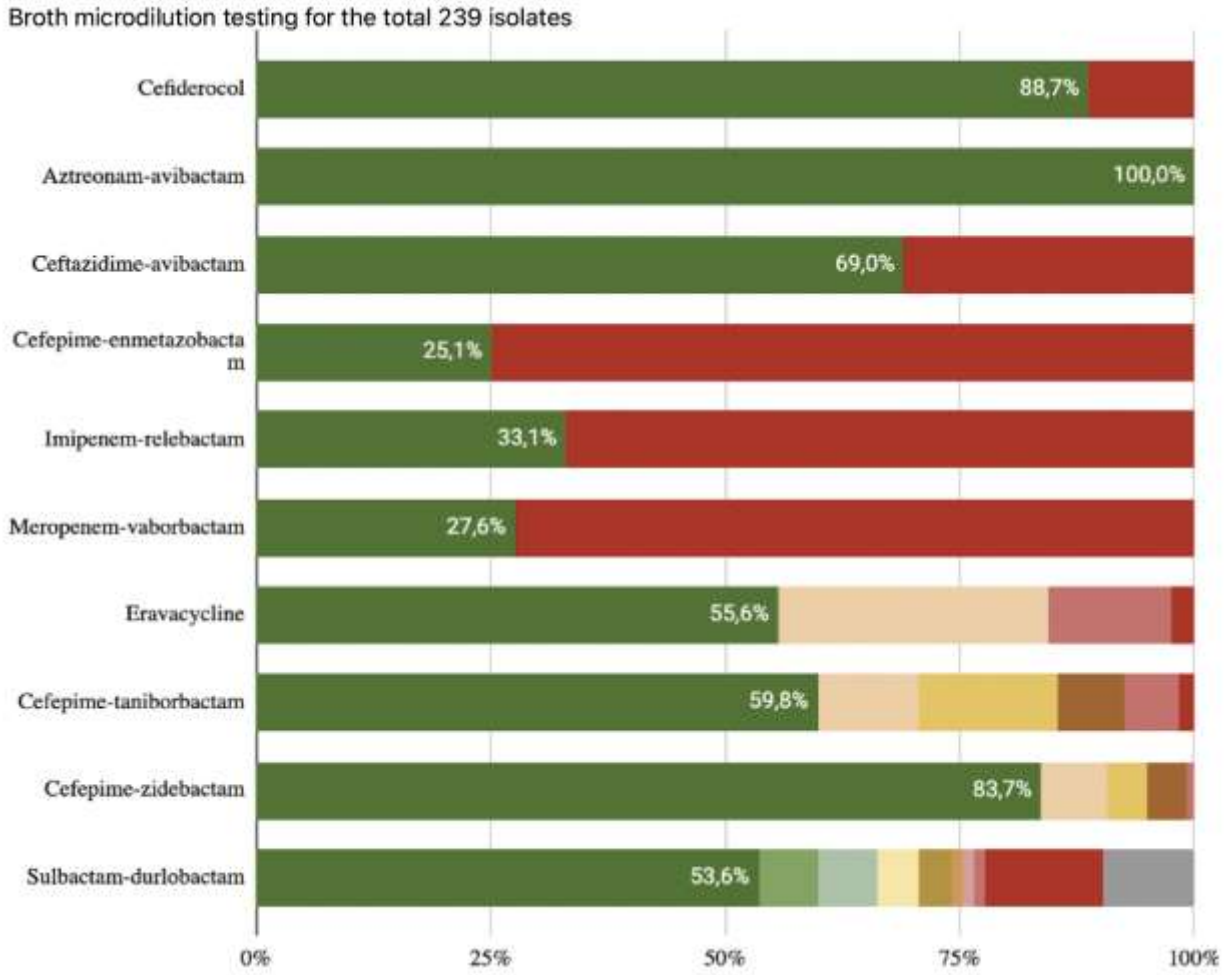
R. Balkaya Demirtaş[1], I.P. Zarakolu[1], G. Hazırolan[1], I. Baltas[2], B. Sobkowiak[2], E. Murrell[2], E. Kiousi[2], A. Laris[2], E. Diver-Hall[2], J. Hatcher[2, 3], L. Grandjean[2], M. Akova[1].

[1]Hacettepe University Medical Faculty - Ankara (Türkiye), [2]UCL Great Ormond Street Institute of Child Health - London (United Kingdom), [3]Great Ormond Street Hospital for Children NHS Foundation Trust - London (United Kingdom)

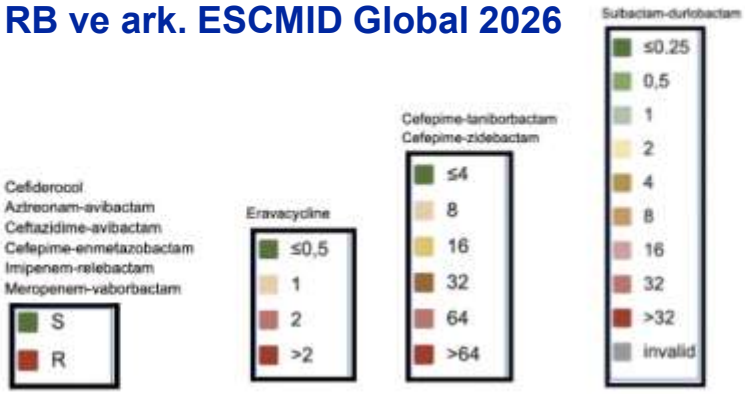
Bakteremik Karbapenem-R *K. pneumonia* İzolatlarının Karbapenemaz Dağılımı Hacettepe 2020-2024



Demirtaş RB ve ark. ESCMID Global 2026



Demirtaş RB ve ark. ESCMID Global 2026



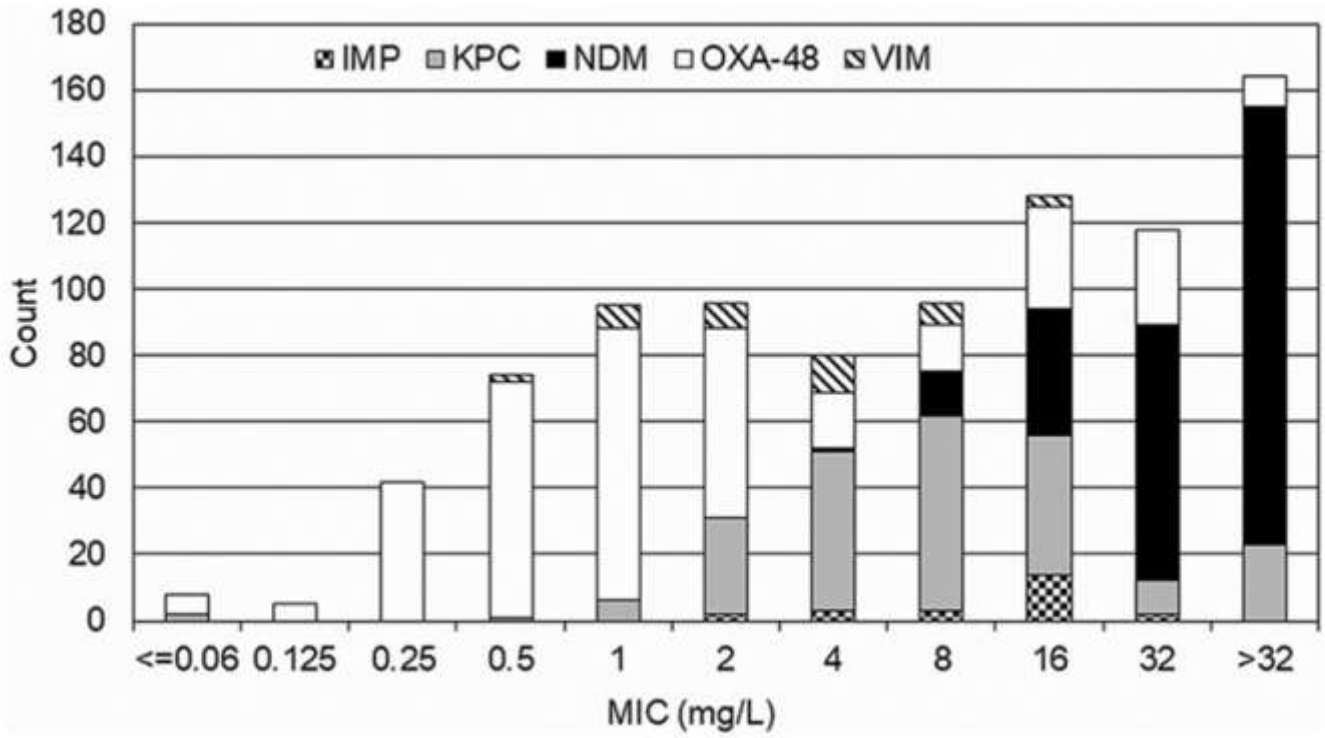
K. pneumoniae
Antibiyotik Duyarlılığı

Antibiotic	MIC (mg/L)	CLSI/FDA	EUCAST
Ertapenem	2	R	R
Imipenem/Meropenem	1	S	S
Ceftazidime	8	I/SDD	R
Cefepime	8	SDD	R
Aztreonam	8	I/SDD	R
Piperacillin-tazobactam	16/4	I/SDD	R
Ceftazidime-avibactam	16/4	R	R
Amikacin	16	R	R
Ciprofloxacin	1	R	R
Colistin	4	R	R

Multipleks PCR Analizi

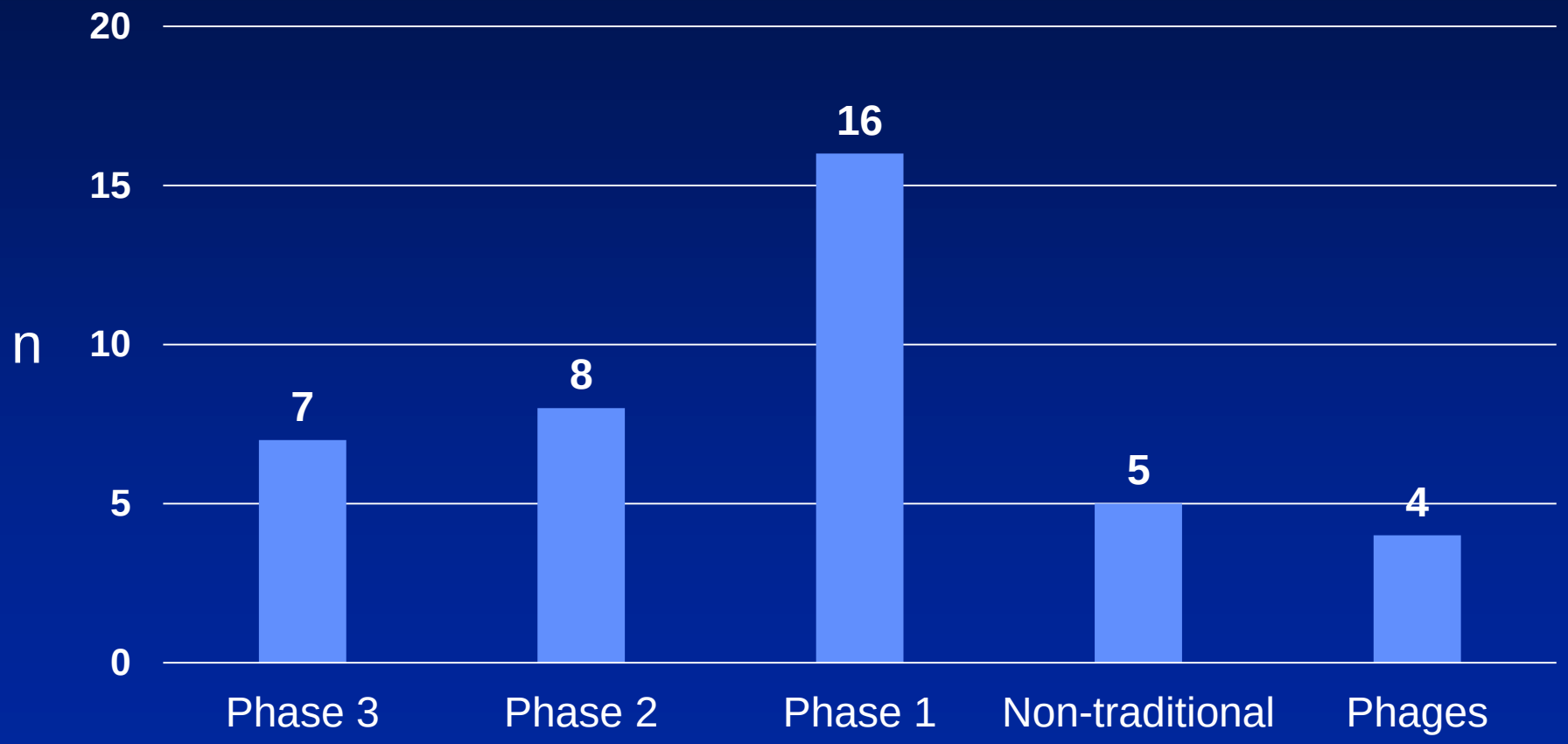
- **OXA-48 ve NDM ve CTX-M 15**

Enterobacterales'de Meropenem MIC Dağılımı



Boyd SE, et al. Antimicrob Agents Chemother 2022;66:1

Klinik Araştırmalarda Yeni Antibiyotikler-2025



Theuretzbacher U. Nat Rev Microbiol 2025;23:491

Yeni Antibiyotiklerin Aktivite Spektrumu

Active
Variable
Not recommended

		Enterobacterales					Lactose non-fermenting organisms	
	Typical dosing regimen for serious infections[111,110,111]	Extended-spectrum β-lactamase-producing Enterobacterales	AmpC β-lactamase-producing Enterobacterales	Ambler class A carbapenemases (eg, KPC and IMI)	Metallo-β-lactamases (eg, NDM, VIM, and IMP)	Ambler class D carbapenemases (eg, OXA-48)	Difficult-to-treat resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*
β-lactam								
Ceftolozane–tazobactam	3 g IV every 8 h, infused over 3 h							
Ceftazidime–avibactam	2·5 g IV every 8 h, infused over 3 h							
Meropenem–vaborbactam	4 g IV every 8 h, infused over 3 h							
Imipenem–relebactam	1·25 g IV every 6 h, infused over 30 min							
Cefiderocol	2 g IV every 8 h, infused over 3 h							
Ceftazidime–avibactam and aztreonam	Ceftazidime–avibactam: 2·5 g IV every 8 h, infused over 3 h plus aztreonam: 2 g IV every 8 h, infused over 3 h*							
Aztreonam–avibactam	2 g/0·67 g loading dose then 1·5 g/0·5 g every 6 h, infused over 3 h							
Cefepime–enmetazobactam	2 g/0·5 g every 8 h, infused over 4 h							
Sulbactam–durlobactam†	1 g of each drug IV every 6 h, infused over 3 h†							
Tetracycline derivative								
Eravacycline	1 mg per kg IV every 12 h							

Macesic N, et al. Lancet 2025;405;257

MDR Gram-negatif Bakteri İnfeksiyonları İçin Kılavuz Önerileri

	IDSA [8**]	ESCMID [7**]	SEIMC [10]	CMA [9]
ESBL-producing Enterobacterales	Carbapenem[a]	Carbapenem[a]		
AmpC β-lactamase-producing Enterobacterales	High risk of clinically significant AmpC production: Cefepime			
Carbapenemase-producing Enterobacterales[b]	Ceftazidime-avibactam (± aztreonam), meropenem-vaborbactam, and imipenem-cilastatin-relebactam	Ceftazidime-avibactam (± aztreonam), meropenem-vaborbactam. Cefiderocol	Ceftazidime–avibactam (± aztreonam), meropenem–vaborbactam, imipenem–relebactam, cefiderocol	Ceftazidime-avibactam (± aztreonam)
Difficult to treat *P. aeruginosa*	Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam. Cefiderocol is an alternative[c]	Ceftolozane-tazobactam	Ceftolozane–tazobactam	
Carbapenem-resistant *A. baumannii*	High-dose ampicillin-sulbactam in combination with at least one other agent	Combination therapy including two in vitro active antibiotics. Susceptible to sulbactam: ampicillin/sulbactam. Resistant to sulbactam: polymyxin, tigecycline	High dose sulbactam in combination with additional antimicrobials	Sulbactam combination therapy. Tigecycline- or polymyxin-based combination therapy (pneumonia caused by CRAB). Choice of therapy regimen should be made according to patient's condition
Stenotrophomonas maltophilia	Combination therapy: TMP-SMX, minocycline/tigecycline, cefiderocol or levofloxacin; or ceftazidime-avibactam and aztreonam[d]	Combination therapy: TMP-SMX and levofloxacin		

Viasus D, et al. Curr Opinon Infect Dis 2024;30:448

Aztreonam
In vitro Aktivitesi

- Metallo beta-laktamazaların hidrolitik aktivitesine dirençli
- Ancak ESBL'ler, KPC karbapenemazlar ve AmpC tarafından inaktive edilir
  - Avibaktam bu inaktivasyonu önler
- Anaerobik ve gram (+) aktivitesi yok

Avibaktam
In vitro Aktivite

- **Grup A, C ve D beta-laktamaz aktivitesi**
  - **ESBL, AmpC ve OXA-48**
- **Aktivite yok**
  - **Metallo enzimler**
  - **Anaeroblar, Gram (+) bakteriler**
  - **Dirençli KPC-3 ve SHV-1 varyantları**
  - ***P. aeruginosa'da «efflux» ve* permeabilite direnci**
  - ***Acinetobacter spp.***

Van Duin D, Bonomo RA. Clin Infect Dis 2016;63:234

Aztreonam-Avibactam (AZT-AVI) REVISIT Çalışması

- AZT-AVI ± metronidazole *vs* Meropenem ± kolistin, 2018-2023
- Ağır gram (-) infeksiyonalr
  - 422 hasta, 282 AZT-AVI, 140 MER
  - 271 hastada en az bir izolat
    - %93 Enterobacterales
    - 19/80 suşta karbapenemaz

Carmeli Y, et al. Lancet Infect Dis 2025;25:218

REVISIT-Sonuçlar

- **Komplike intraabdominal infeksiyon**
  - Klinik kür(AZT-AVI) %45.9 *vs* (MER) %41.7
  - 28. gün mortalite %2 *vs* %3
- **HAP/VAP**
  - %76.4 *vs* %74, klinik kür
  - %11 *vs* %19, 28. gün mortalite
- **Güvenlik**
  - Her iki kolda benzer
    - Ciddi advers olay yok

Carmeli Y, et al. Lancet Infect Dis 2025;25:218

AZT-AVI *vs* MBL (+) Bakteri İnfeksiyonları-ASSEMBLE Çalışması

- AZT-AVI ± metronidazole vs "*best available therapy*" (BAT)
  - cIAI, cUTI, HAP/VAP veya BSI
  - Açık, randomize, 2:1
  - Primer sonlanım, klinik kür 28 ± 3 gün
- Sadece 15 hasta randomize edilmiş
  - 12 AZT-AVI, 3 BAT
    - K. pneumonia 6/12 *vs* 2/3 izolatta
  - Klinik kür 5/12 (%42) *vs* 0/3
  - 28-gün mortalite 1/12 (%8) vs 1/3 (%33)

Daikos G, et al. JAC Antimicrob Resist 2025;7(4):dlaf131

Cefiderecol

- **APEKS-NP Çalışması**
  - *vs* yüksek doz meropenem, nozokomiyal pnömoni
- **CREDIBLE Çalışması**
  - *vs* «*best available tx*» CR-GNB infeksiyonlar
- **Rakamsal olarak MBL (+)lere karşı etkin**
  - Klinik kür17/24 vs 4/10
  - Mikrobyolojik eradikasyon 14/24 vs 4/10
  - Düşük 28 günlük mortalite
  - Acinetobakter infeksiyonlarında yüksek mortalite
- **NDM üreten bakteriler dirençli**

Wunderink RG, et al. Lancet Infect Dis 2021;21:2013
Bassetti M, et al. Lancet Infect Dis 2021;21:226

Cefiderocol versus standard therapy for hospital-acquired and health-care-associated Gram-negative bacterial bloodstream infection (the GAME CHANGER trial): an open-label, parallel-group, randomised trial

Lancet Infect Dis

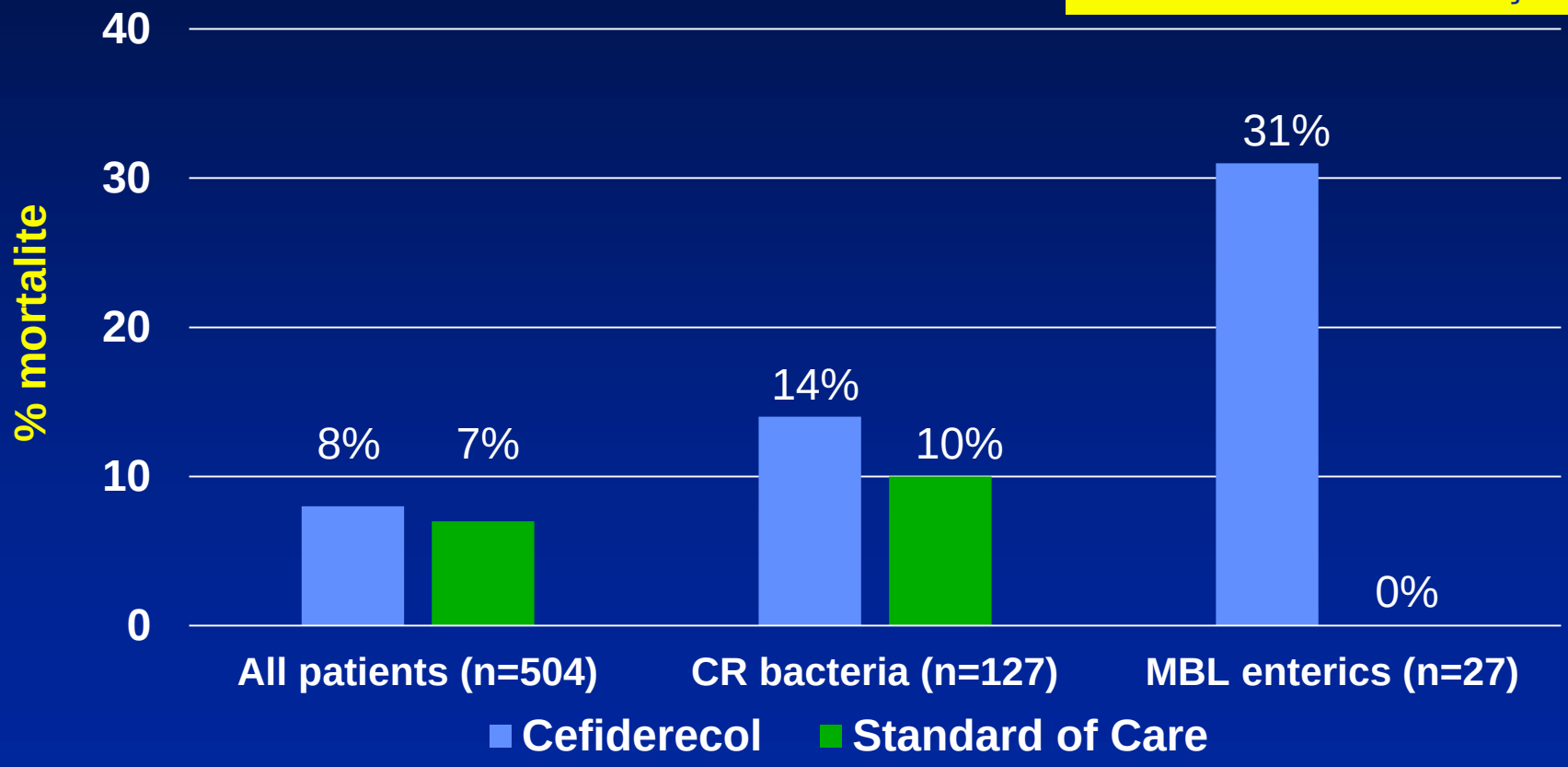
2026 Feb;26:148-59

*David L Paterson, Helmi Sulaiman, Po-Yu Liu, Mark D Chatfield, Mesut Yilmaz, Zeti Norfidiyati Salmuna, Mohd Zulfakar Mazlan, Siriluck Anunnatsiri, Rujipas Sirijatuphat, Darunee Chotiprasitsakul, David C Lye, Jyoti Somani, Shirin Kalimuddin, Abdullah T Aslan, Visanu Thamlikitkul, Yi-Tzu Lee, Ya-Sung Yang, Yi-Tsung Lin, Wan Nurliyana Wan Ramli, Chien-Hao Tseng, Sophia Archuleta, Yvonne Fu Zi Chan, Brian M Forde, Hugh Wright, Adam G Stewart, Kay A Ramsay, Weiping Ling, Vicki Rossi, Tiffany M Harris-Brown, Patrick N A Harris, on behalf of the GAME CHANGER Trial Investigators**

- **Açık, parellel, randomize, çok merkezli**
- **Gr (-) bakteremi, 17 merkez, 2019-2023 arası**
  - **Cefiderecol (CFD) vs standart bakım (SoC) tedavisi**
  - **Primer sonlanmı 14- gün mortalite**
  - **Non-inferiorite sınırı %10**
- **504 hasta**
  - **250 hasta CFD kolunda**
  - **254 hasta SoC kolunda**

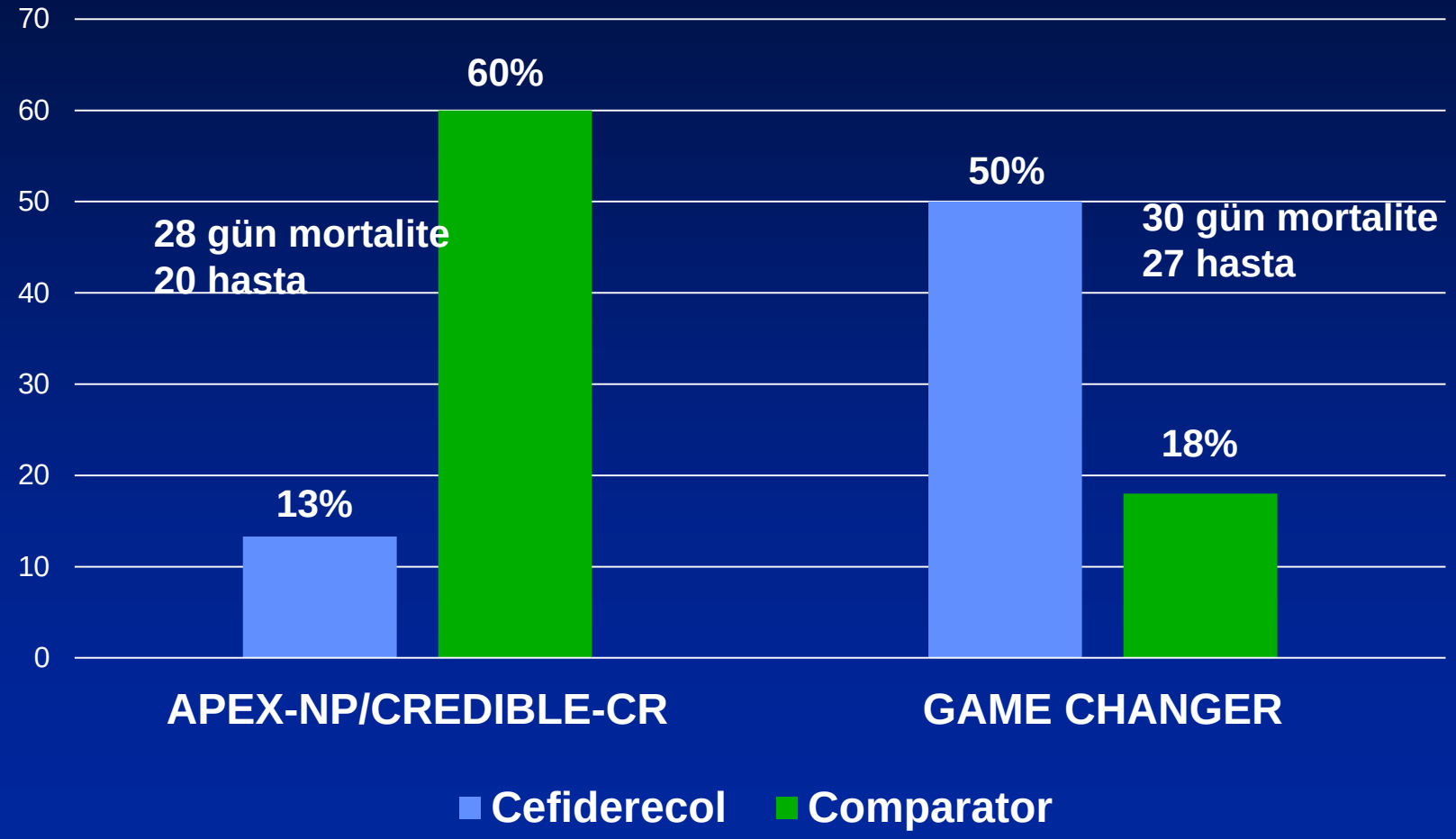
GAME CHANGER Çalışması
14 Günlük Mortalite

15/27 (%56) MBL (+) enterik Cefiderecol dirençli



Paterson DL, et al. Lancet Infcet Dis 2026;26:148

Cefiderecol vs MBL-Sentezleyen *Enterobacterales*



Timsit JF, et al. Clin Infect Dis 2022;75:1081

Paterson DL, et al. Lancet Infect Dis 2025, October 6

Ceftolozane

- Ceftolozane bir «oximino cephalosporin» yapısal olarak seftazidim'e benzer
  - AmpC indüksiyonu zayıf
  - *P. aeruginosa'da* Mex efflux pompaları için zayıf bir substrat
  - ESBL stabilitesi zayıf

Giacobbe DR, et al. Expert Rev Anti Infect Ther 2018;16:307

Ceftolozane Tazobactam

- Dereprese AmpC sentezleyen *P. aeruginosa* aktivitesi yüksek
  - OprD porin kaybından etkilenmez
  - Tazobaktam ESBL direncini sağlar
  - Ceftolozane OXA-1'e karşı aktif
    - OXA-48 dışında karbapenemaz aktivitesi yok
- Aktivite yok
  - Stafilokok ve enterokoklar
  - *Bacteroides* hariç anaeroblar

Giacobbe DR, et al. Expert Rev Anti Infect Ther 2018;16:307

Ceftolozane Tazobactam Klinik Kullanım

- HAP/VAP, cUTI ve cIAI (metronidazole ile) için FDA ve EMA onaylı
  - VAP ve cIAI çalışmalarında meropenem'e karşı «non-inferior»
  - cUTI çalışmasında levofloksasine karşı üstün

Giacobbe DR, et al. Expert Rev Anti Infect Ther 2018;16:307
Kollef MH, et al. Lancet Infect Dis 25 September 2019. pii: S1473-3099(19)30403-7

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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)

Prof Keith S Kaye, MD • Prof Andrew F Shorr, MD • Prof Richard G Wunderink, MD • Prof Bin Du, MD • Gabrielle E Poirier, BS • Khurram Rana, PharmD • et al. Show all authors

Published: May 11, 2023 • DOI: https://doi.org/10.1016/S1473-3099(23)00184-6 • Check for updates

ATTACK Çalışması
Sulbactam Durlobactam vs Colistin

- 2019-2022,181 hasta
  - Tüm hastalara imipenem-cilastatin verilmiş
  - 176 HAP, VAP
  - 5 CRAB bakteremisi
  - 125 hastada etkinlik analizi
  - 28 günlük mortalite
    - %19 SUL-DUR, % 32 COL
      - (-13.2%, 95% CI -30.0 to 3.5), non-inferior
  - Nefrotoksisite
    - %13 vs %38 (p>.001)

Kaye KS, et al. Lancet Infect Dis 2023;23:1072

Table 2. Antimicrobial activity of sulbactam/durlobactam against *Acinetobacter* tested isolates.

Isolates Characteristics	Susceptible to SUL/DUR (%)	Resistant to SUL/DUR (%)
A. baumannii complex (n = 9754)	9530 (97.7%)	224 (2.3%)
CRAB (n = 5812)	5614 (96.6%)	198 (3.4%)
Colistin-resistant (n = 507)	488 (96.2%)	19 (3.7%)
NDM-1 producers (n = 28)	0 (0%)	28 (100%)

CRAB: carbapenem-resistant *Acinetobacter baumannii* complex; SUL/DUR: sulbactam/durlobactam.

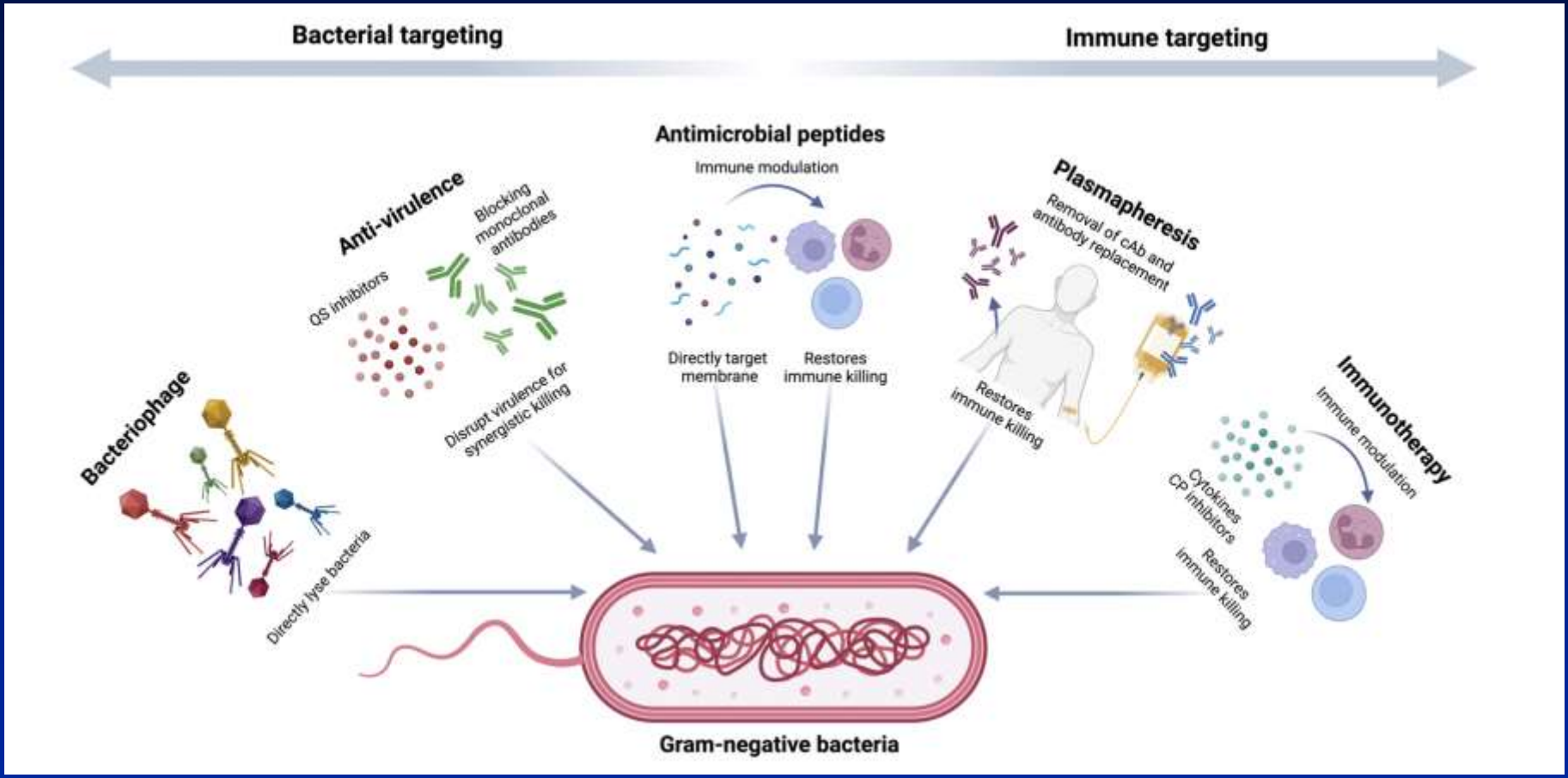
Principe L, et al. Antibiotics 2022;11:1793

Faz III Aşamasında Yeni Antibiyotikler

Phase	Agent (developer)	Antibacterial class	Formulation and indication	Chemical class	Target	Spectrum	Susceptibility and resistance
III	Cefepime–taniborbactam (VenatoRx, Melinta, GARDP, Menarini Group, Everest Medicines)	Cephalosporin–boronate BLI	i.v.; cUTI	Old chemical class	Old target	Enterobacterales, *P. aeruginosa*	CRE: >90% susceptible CRPA: ~70% susceptible Resistance: IMP, mutations in PBP3, porins, upregulation of efflux pumps, accumulation of multiple resistance mechanisms
	Gepotidacin[a] (GSK)	NBTI (triazaaceanaphthylene)	Oral; uUTI, uGon	New chemical class	New bacterial target/binding site	*N. gonorrhoeae*, Enterobacterales	CRE: >90% susceptible NG: ~100% susceptible Resistance: risk of cross-resistance in Enterobacterales unknown, requires double mutations that have been shown in NG
	Zoliflodacin (Innoviva, GARDP)	NBTI/GyrB inhibitor (spiropyrimidenetrione)	Oral; uGon	New chemical class	New bacterial target/binding site	Gram+, *N. gonorrhoeae*	NG: ~100% susceptible Resistance: mutation in GyrB
	Imipenem/cilastatin–funobactam (Evopoint Biosciences)	Carbapenem/dehydropeptidase inhibitor–DBO BLI	i.v.; cUTI, HAP–VAP	Old chemical class	Old target	Enterobacterales	CRE: susceptibility unknown, no activity against MBL-producing strains, similar to imipenem–relebactam
	Cefepime–zidebactam (Wockhardt)	Cephalosporin–DBO BLI and PBP2	i.v.; cUTI	Old chemical class	Old target	Enterobacterales, *P. aeruginosa*	CRE: >90% susceptible CRPA: >90% susceptible Resistance: in *P. aeruginosa*, mutations in PBP2, PBP3, porins, upregulation of efflux pumps, risk of cross-resistance unclear
	Cefepime or aztreonam–nacubactam (Meiji)	Cephalosporin or monobactam–DBO BLI and PBP2	i.v.; cUTI	Old chemical class	Old target	Enterobacterales, *P. aeruginosa*	CRE: >90% susceptible CRPA: >90% susceptible (combination with cefepime) Resistance: similar to cefepime/zidebactam
	Tebipenem pivoxil (Spero Therapeutics, GSK)	Carbapenem	Oral; cUTI	Old chemical class	Old target	Enterobacterales	CRE: resistant ESBL-producing Enterobacterales: >90%

Theuretzbacher U. Nat Rev Microbiol 2025;23:491

Antibiyotik Dışı Tedavi Yöntemleri



Hickson SM, et al. NPJ Antimicrob Resist 2025;3:16

Sonuç

- Gram-negative bakterilerde çoklu direnç giderek artan önemli bir sorun
  - Özellikle karbapenem direnci ve XDR/PDR fenotipi
  - MBL aracılı direnç sık bir sorun
- Lokal epidemiyolojik farklılıklar empirik tedavi açısından önemli
- Yeni antibiyotikler soruna tam yanıt oluşturmasa da, tedavideki rolleri önemli
- Özellikle MBL aracılı infeksiyonlar için randomize kontrollü çalışmalara gerek var

Teşekkürler…