Gram Negatif Enfeksiyonlarda Yeni Tedavi Seçenekleri

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Bursa Uludağ Üniversitesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

WHO-Acil Yeni Antibiyotik İhtiyacı

- 2017
- Öncelik: Kritik, Yüksek, Orta
- Kritik Grup: ÇİD bakteriler
  - -Enterobacteriaceae (ESBL, CR)
  - -CR-*Acinetobacter* *baumannii*
  - -CR-*Pseudomonas* aeruginosa

Tablo 24. Türkiye'de Sağlık Hizmeti İlişkili Enfeksiyonlarda Antimikrobiyal Direnç Oranları, 2020.

ANTİMİKROBİYAL DİRENÇLİ PATOJEN	Antimikrobiyal Direnç Oranları				PERSENTİL				
	Hastane Sayısı†	Toplam Etken Sayısı	Dirençli Etken Sayısı	Ağırlıklı Genel Ortalama	% 10	% 25	% 50 (Ortanca)	% 75	% 90
TÜRKİYE GENELİ									
Vankomisin dirençli *E. faecium*	194(38)	1614	285	17.66	0.00	4.11	16.67	28.35	50.16
Vankomisin dirençli *E. faecalis*	192(34)	1444	41	2.84	0.00	0.00	0.00	3.66	10.38
MRSA	305(55)	2243	880	39.23	17.91	28.13	39.20	55.0	72.0
MRKNS	285(72)	2619	1742	66.51	19.36	59.77	74.54	82.03	94.62
E. coli Suşlarında ESBL	415(111)	4185	1867	44.61	2.24	30.77	52.94	65.57	81.44
Klebsiella pneumoniae Suşlarında ESBL	378(168)	8109	4074	50.24	1.55	23.50	55.40	74.92	87.36
Karbapenem dirençli *Acinetobacter baumannii*	361(172)	7886	5771	73.18	26.73	65.21	82.68	90.91	95.81
Karbapenem dirençli *Pseudomonas aeruginosa*	374(99)	3735	1484	39.73	6.25	23.53	36.76	56.25	70.00
Karbapenem dirençli *Klebsiella pneumoniae*	378(169)	8174	4001	48.95	15.22	33.57	48.65	66.03	78.57
Kolistin dirençli *Acinetobacter baumannii*	361(171)	7854	305	3.88	0.00	0.00	1.43	6.02	14.22
Kolistin dirençli *Klebsiella pneumoniae*	378(167)	8100	980	12.10	0.00	2.53	8.33	18.18	31.87

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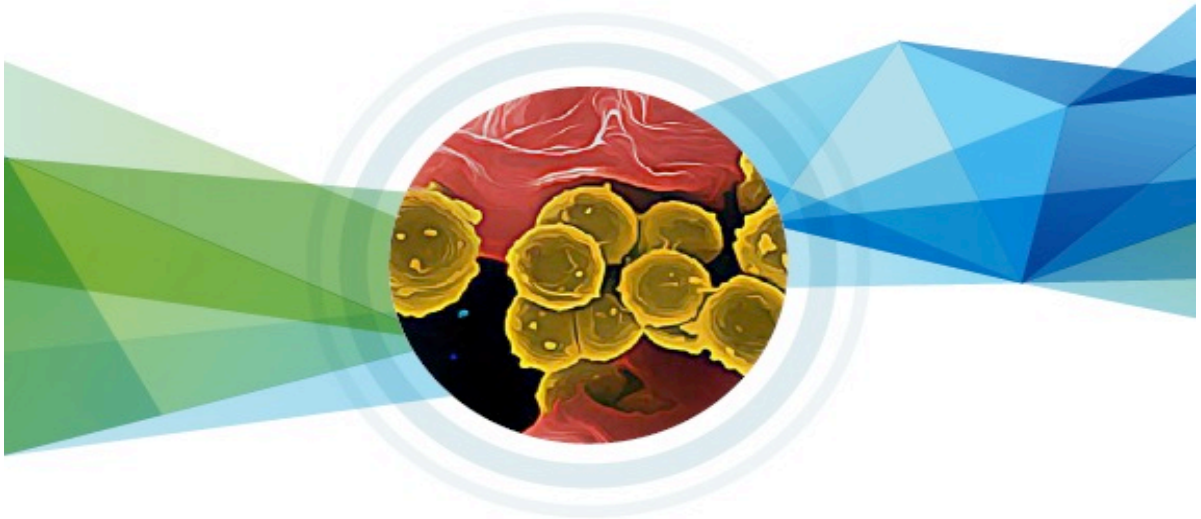
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

World Health Organization
REGIONAL OFFICE FOR Europe

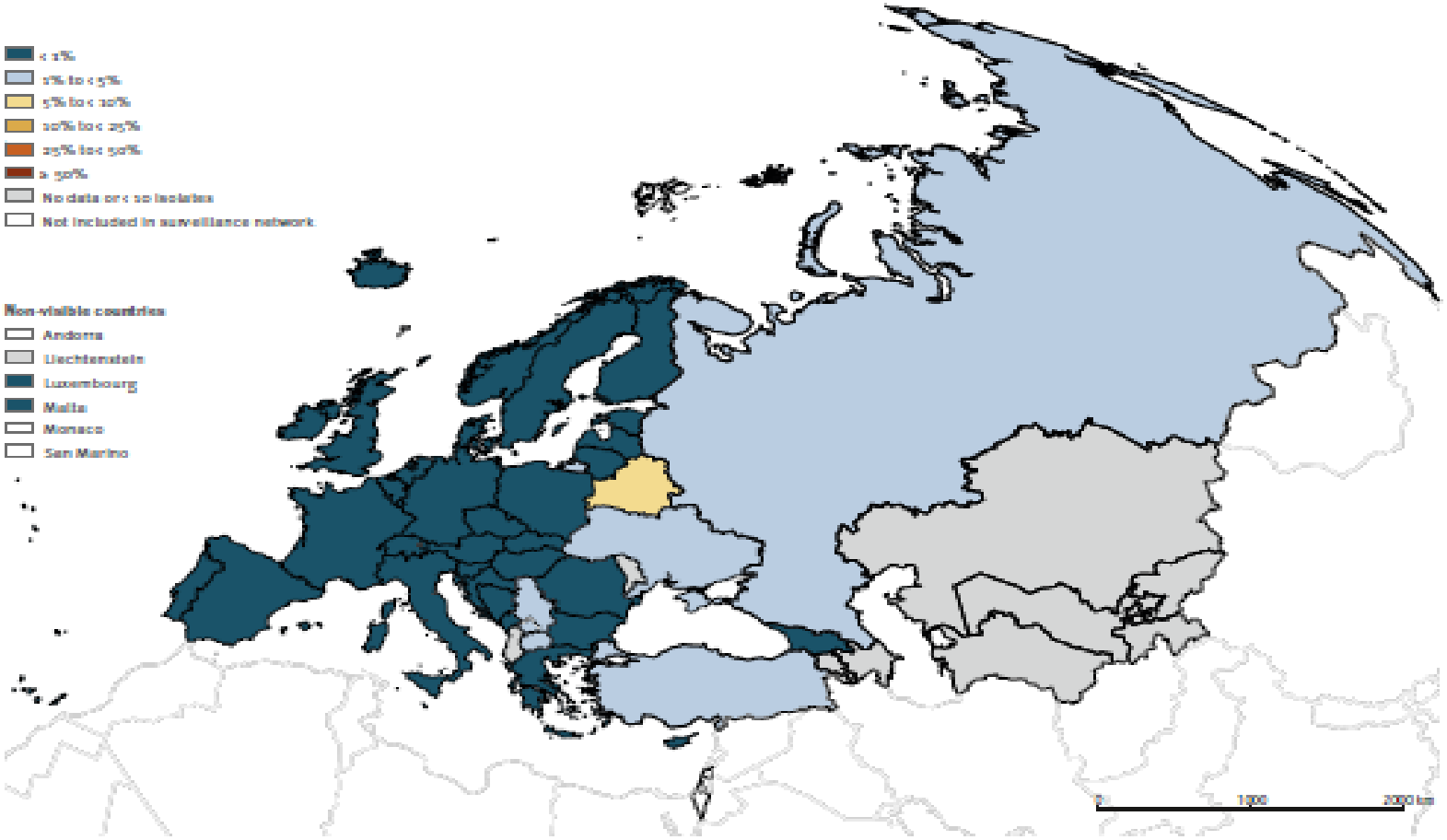


Antimicrobial resistance surveillance in Europe

2022

2020 data

Fig. 3 *E. coli*: percentage of invasive isolates resistant to carbapenems (Imipenem/meropenem), by country/area, WHO European Region, 2020

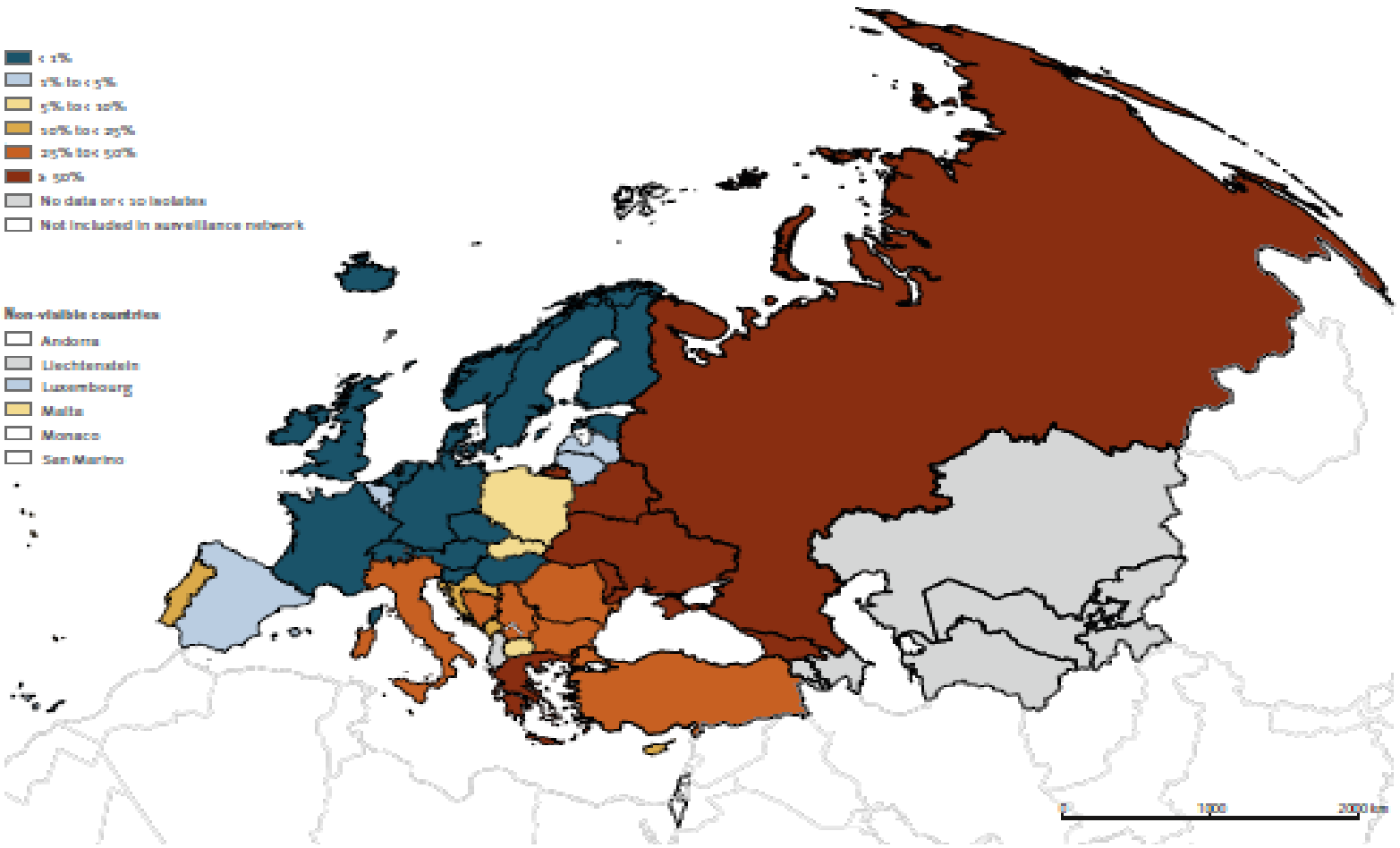


Note: data for Serbia and Kosovo (All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999)) were combined for this map. Data for the United Kingdom for 2020 do not include Scotland and Wales.

Data sources: 2020 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2021. All rights reserved.) and 2020 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2021).
Map production: ©WHO.

E. coli – Karbapenem Direnci

Fig. 5 *K. pneumoniae*: percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



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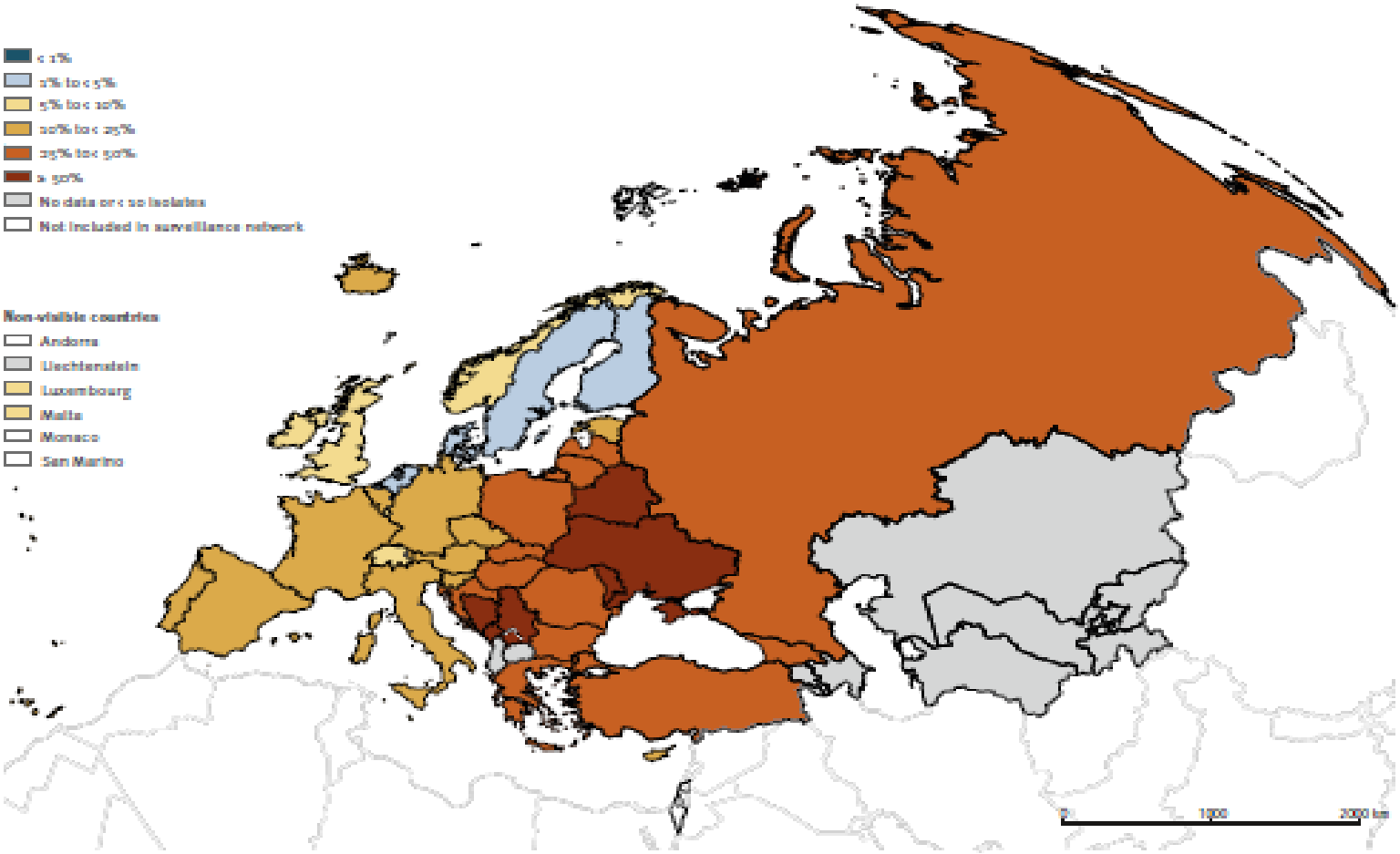
K. pneumoniae – Karbapenem Direnci

Fig. 6 *P. aeruginosa*: percentage of invasive isolates with resistance to carbapenems (Imipenem/meropenem), by country/area, WHO European Region, 2020



Note: data for Serbia and Kosovo (All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999)) were combined for this map. Data for the United Kingdom for 2020 do not include Scotland and Wales.

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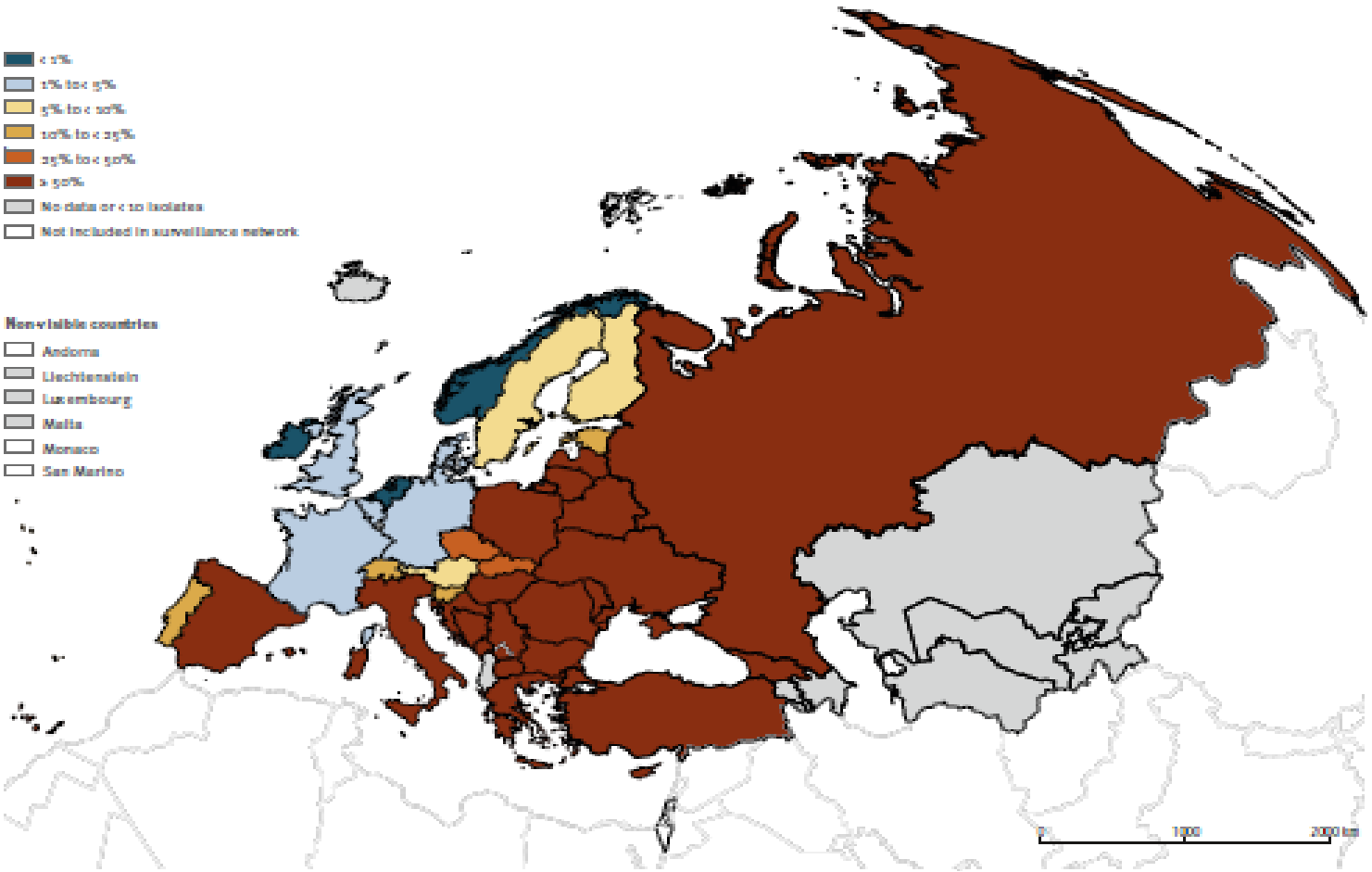
Map production: ©WHO.

P. aeruginosa – Karbapenem Direnci

Fig. 7 *Acinetobacter* spp.: percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country/area, WHO European Region, 2020



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Map production: ©WHO.

A. baumannii - Karbapenem Direnci

Boral et al. Ann Clin Microbiol Antimicrob (2019) 18:19
https://doi.org/10.1186/s12941-019-0319-8

Annals of Clinical Microbiology and Antimicrobials

RESEARCH Open Access

A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant *Acinetobacter baumannii* infections in intensive care units with clinical and environmental features

Baris Boral[1], Özlem Unaldi[2], Alper Ergin[3], Riza Durmaz[2,4], Özgen Köseoğlu Eser[1*] and the Acinetobacter Study Group

Table 3 Antimicrobial susceptibility of invasive MDR *A. baumannii* isolates from ICUs ($n = 172$)

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	Resistance (%)
Amikacin	≥ 256	≥ 256	1 to ≥ 256	91.8
Ampicillin–sulbactam	256	≥ 256	32 to ≥ 256	99.4
Ceftazidime	256	≥ 256	16 to ≥ 256	99.4
Ciprofloxacin	128	≥ 256	8 to ≥ 256	100
Imipenem	64	128	1 to ≥ 256	99.4
Colistin	0.5	1.0	0.25–64	1.2
Tigecycline	1.0	2.0	0.01–3	1.7

Özgün Çalışma/Original Article | Mikrobiyol Bul 2021;55(1):1-16/doi: 10.5578/mb.20124

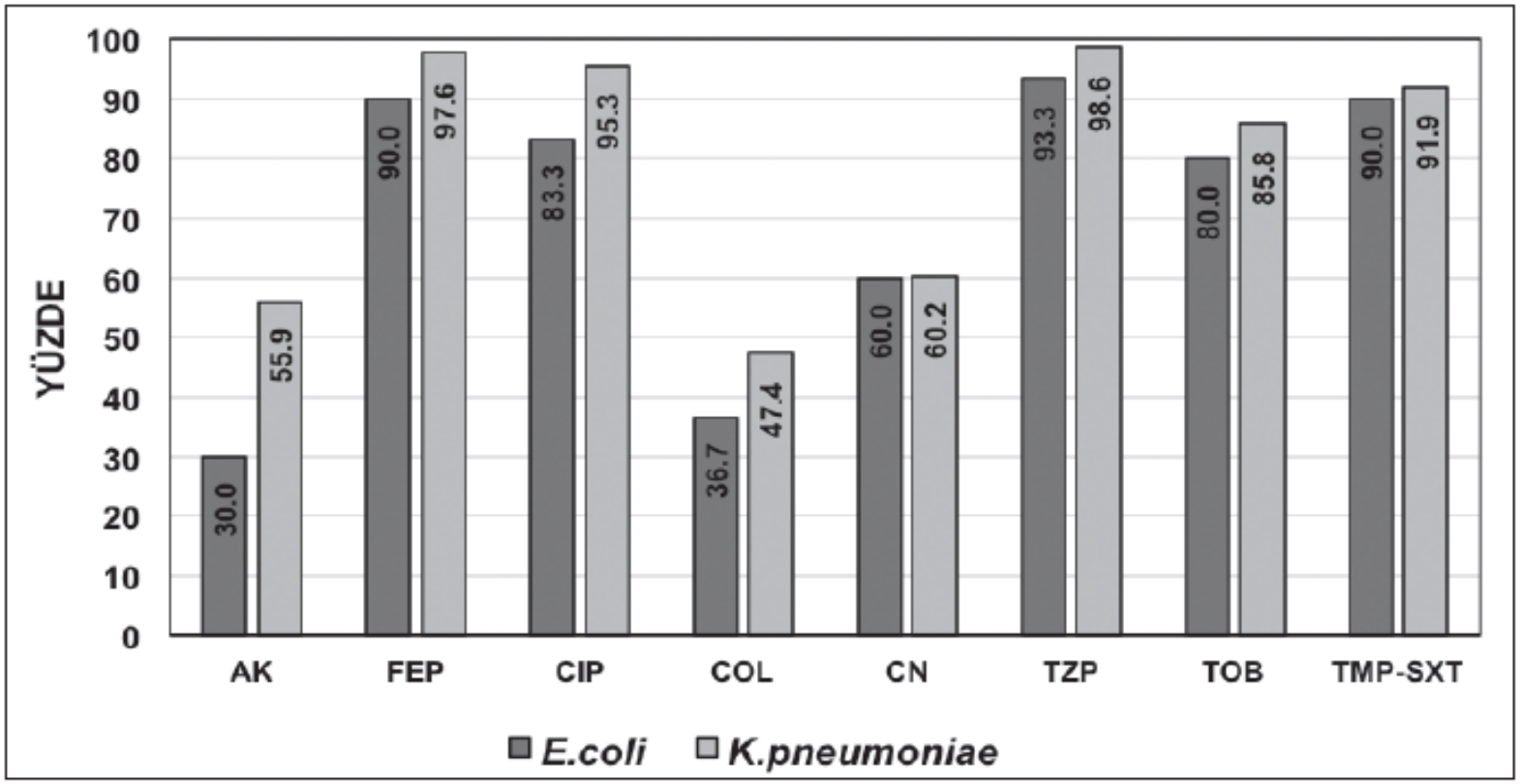
Geliş Tarihi (Received): 25.05.2020 • Kabul Ediliş Tarihi (Accepted): 19.11.2020

Türkiye'de 2019 Yılı İçinde İzole Edilen *Escherichia coli* ve *Klebsiella pneumoniae* İzolatlarında Karbapenemaz Epidemiyolojisi

The Epidemiology of Carbapenemases in *Escherichia coli* and *Klebsiella pneumoniae* Isolated in 2019 in Turkey

Serap SÜZÜK YILDIZ[1](ID), Hüsniye ŞİMŞEK[1](ID), Zekiye BAKKALOĞLU[1](ID), Yasemin NUMANOĞLU ÇEVİK[1](ID), Can Hüseyin HEKİMOĞLU[1](ID), Selçuk KILIÇ[1](ID), Emine ALP MEŞE[2](ID), Ulusal Karbapenemaz Sürveyans Çalışma Grubu*

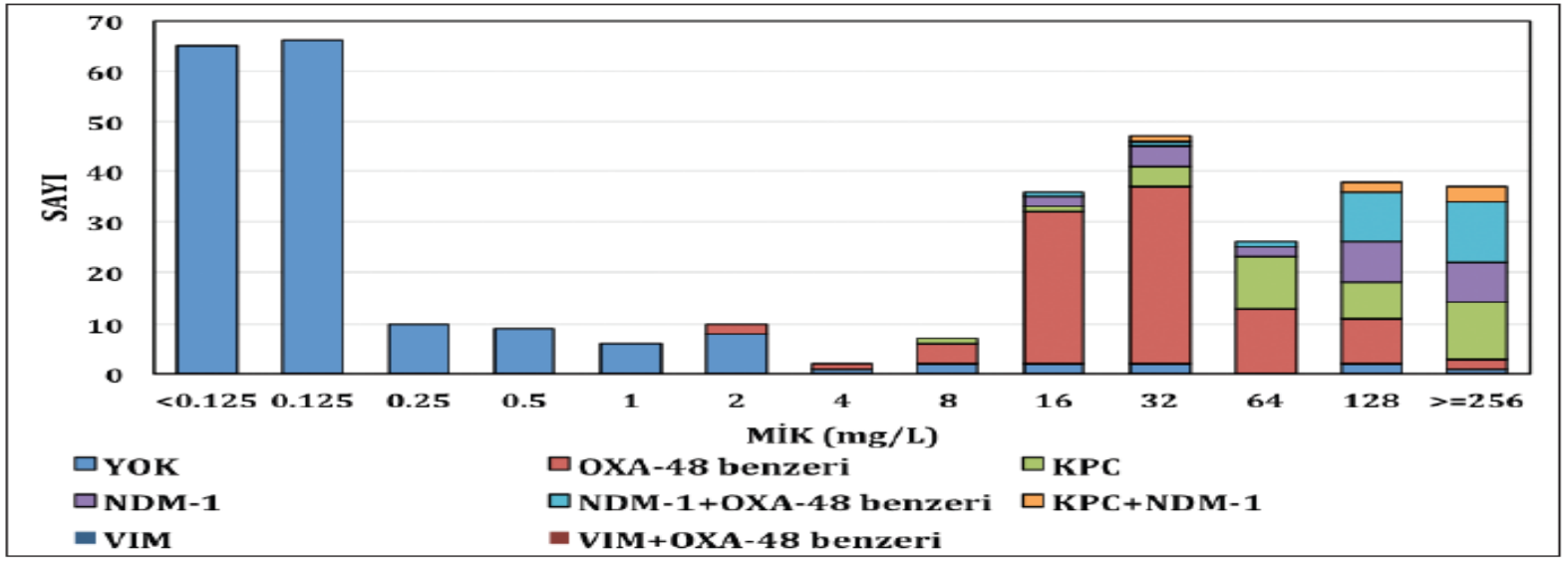
- 2019 yılı izolatları
- 26 Hastane
- 127 *E.coli* ve 366 *K.pneumoniae*
- %69 Hastane kökenli
- 245(%49.7) Karbapenem dirençli



Şekil 3. *Karbapenem dirençli izolatların farklı antibiyotiklere karşı direnç yüzdeleri.*

AK: Amikasin, FEP: Sefepim, CIP: Siprofloksasin, COL: Kolistin, CN: Gentamisin, TZP: Piperasilin tazobaktam, TOB: Tobramisin, TMP-SXT: Trimetoprim sülfametoksazol.

- Toplam olarak izolatların %23.3'ünde kolistin direnci
- *mcr* 1-8 yok



Şekil 6. K.pneumoniae izolatlarının meropenem MİK dağılımlarına göre karbapenemaz enzim tipinin dağılımı.

- Karbapenemlerden en az birine dirençli olan olan izolatlarda saptanan karbapenemaz tipleri
  - -OXA-48(%52.2)
  - -KPC(%16.1)
  - -NDM-1(%15)
  - -OXA-48 + NDM-1(%12.6)
  - -KPC + NDM-1(%2.8)
  - -VIM(1 izolat, %0.5)
  - -OXA-48 + VIM(1 izolat, %0.5)

Pseudomonas aeruginosa

- VIM, IMP-1

  Özgümüş OB et al. Microb Drug Resist 2007

- VIM-2

  Yakupoğulları Y et al. J Antimicrob Chemother 2007

- VIM-5

  Bahar G et al. J Antimicrob Chemother 2004

- VIM-5 + IMP-7

  Çekin ZK et al. Diagn Microbiol Infect Dis 2021

Emerging Microbes & Infections
2020, VOL. 9
https://doi.org/10.1080/22221751.2020.1713025

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LETTER

Co-existence of OXA-48 and NDM-1 in colistin resistant *Pseudomonas aeruginosa* ST235

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[a]Department of Infectious Diseases and Clinical Microbiology, Koc University School of Medicine, Istanbul, Turkey; [b]Department of Infectious Diseases and Clinical Microbiology, Kosuyolu State Hospital, Istanbul, Turkey

ABSTRACT

Here, we presented 11 cases with colistin-resistant *Pseudomonas aeruginosa* infection and co-existence of OXA-48 and NDM-1 in the ST235 high-risk clone. The molecular analyses were performed by Sanger sequencing and RT–PCR. The eight patients (72.7%) had an invasive infection and three (27.3%) had colonization. The 30-day mortality rate was 87.5% (7/8). Three patients (37.5%, 3/8) received colistin therapy before isolation of *P. aeruginosa*. In the Multilocus sequence typing (MLST) analysis of 11 isolates, eight (72.7%) isolates belonged to *P. aeruginosa* ST235 clone. All isolates were NDM-1 positive, and nine isolates (81.8%) were found to be positive for both OXA-48 and NDM-1. Sequences of *pmrAB* and *phoPQ* revealed numerous insertions and deletions in all isolates. In 10 isolates *pmrAB* and *phoPQ* were found to be upregulated. In conclusion, the co-existence of OXA-48 and NDM-1 genes in colistin-resistant *P. aeruginosa* ST235 high-risk clone indicates the spread of carbapenemases in clinical isolates and highlights need of continuous surveillance for high-risk clones of *P. aeruginosa*.

Table 1. Clinical and laboratory characteristics of study population.

Code	ST	Source	Colistin MIC	Meropenem MIC	Carbapenemase	Empirical Therapy	Pre-exposure time to colistin	Active Therapy	Duration of Active Colistin Therapy	Survival	30-day Mortality	Clonal Relatedness
K704	235	Catheter	>64	16	OXA-48, NDM-1	Meropenem Vancomycin	0	0	0	Ex	1	
K741	235	BAL	16	16	OXA-48, NDM-1	Moxifloxacin	0	Meropenem Colistin Ertapenem	1	Ex	2	*
K740	3078	BAL	>64	8	OXA-48, NDM-1	Piperacillin Tazobactam	0	Meropenem Colistin Ertapenem	27	Ex	30	
K748	235	DTA	64	16	OXA-48, NDM-1	0	0	0	0	Discharge	Discharge	*
K752	3078	DTA	4	16	OXA-48, NDM-1	0	0	0	0	Discharge	Discharge	**
K753	3078	BAL	4	8	OXA-48, NDM-1	Piperacillin Tazobactam	0	Meropenem Colistin	14	Discharge	Discharge	**
K783	235	BAL	16	16	OXA-48, NDM-1	Meropenem Colistin	10	Meropenem Colistin	10	Ex	7	
K970	235	Catheter	32	16	NDM-1	Levofloxacin Colistin	21 days	0	0	Ex	10	
K982	235	BAL	16	16	OXA-48, NDM-1	Colistin (inhalation)	25 days	0	0	Ex	1	
K989	235	Catheter	>64	16	NDM-1	Meropenem	0	Meropenem Colistin	38	Ex	42	
K1009	235	DTA	16	16	OXA-48, NDM-1	Colistin (inhalation)	8 days	0	0	Ex	19	

Notes: BAL: Bronchoalveolar lavage; DTA: Deep tracheal aspirate.
*clone 1, **clone 2.

Acinetobacter baumannii

- OXA-58, OXA-23

  Gür D et al. J Med Microbiol 2008

- OXA-51, OXA-58

  Vahaboğlu H et al. J Antimicrob Chemother 2006

Boral et al. Ann Clin Microbiol Antimicrob (2019) 18:19
https://doi.org/10.1186/s12941-019-0319-8

Annals of Clinical Microbiology and Antimicrobials

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A prospective multicenter study on the evaluation of antimicrobial resistance and molecular epidemiology of multidrug-resistant *Acinetobacter baumannii* infections in intensive care units with clinical and environmental features

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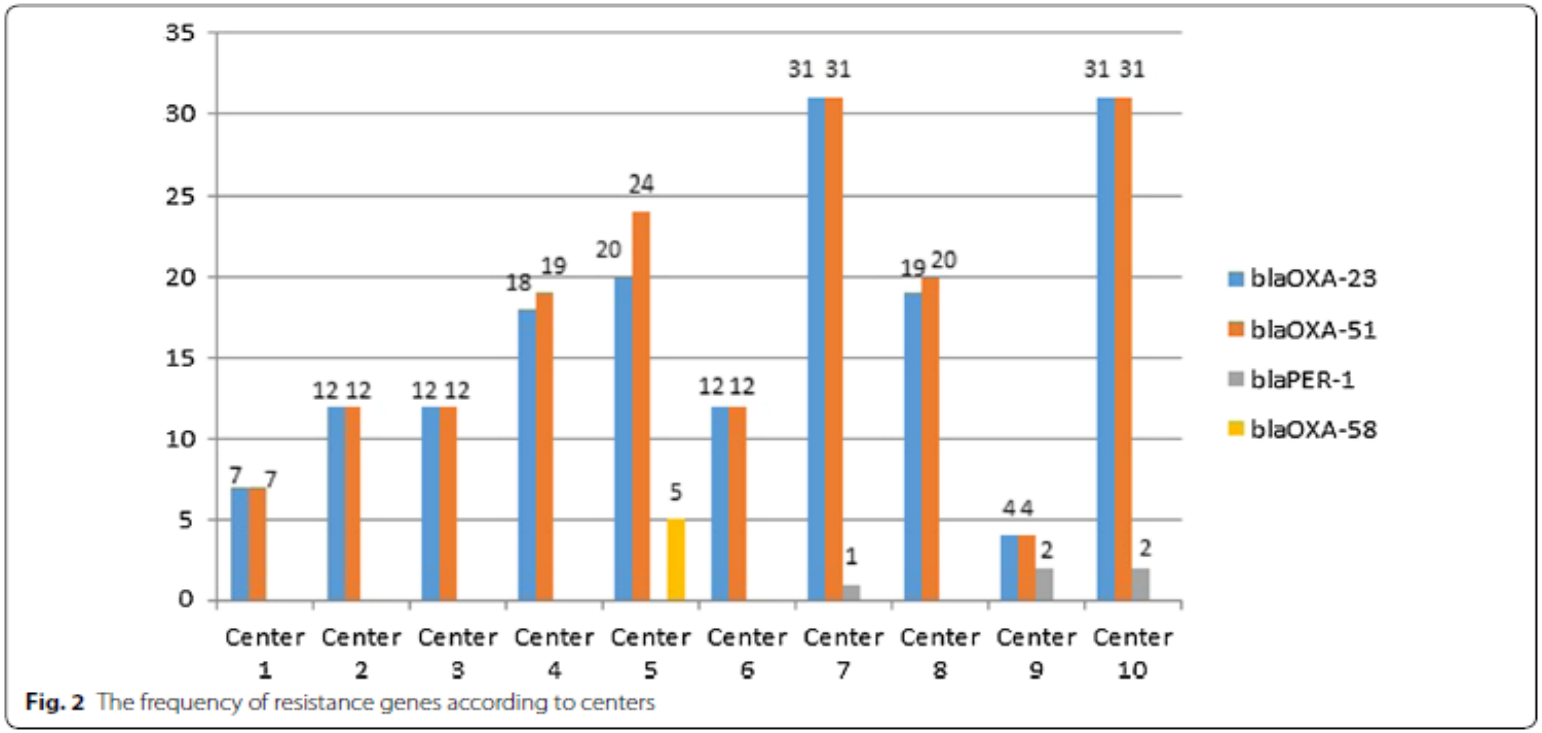

Fig. 2 The frequency of resistance genes according to centers

Antibiotic Agents Approved, 1983-2004

Source: Spellberg et al., *CID*, May 1, 2004 (modified)

Bad Bugs Need Drugs

10x'20

Ten new **ANTIBIOTICS** by 2020

Acta Microbiol Immunol Hung. 2021 Jul 29. doi: 10.1556/030.2021.01525. Online ahead of print.

Ceftazidime – Avibactam susceptibility among carbapenem-resistant Enterobacterales in a pilot study in Turkey

Hasan Selcuk Ozger [1], Ebru Evren [2], Serap Suzuk Yildiz [3], Cigdem Erol [4], Fatma Bayrakdar [3], Ozlem Azap [4], Alpay Azap [5], Esin Senol [1]

Affiliations
PMID: 34324428 DOI: 10.1556/030.2021.01525

Abstract

This study aimed to detect carbapenemase genes and to determine the in vitro susceptibility of Ceftazidime-Avibactam (CZA) in Enterobacterales isolates. Carbapenemase genes were detected by polymerase chain reaction. CZA sensitivity of isolates was evaluated with broth microdilution (BMD) and disk diffusion methods. A total of 318 carbapenem-resistant Enterobacterales isolates were included. Most of the isolates (n = 290, 91.2%) were identified as Klebsiella pneumoniae. The most common carbapenemase type was OXA-48 (n = 82, 27.6%). CZA susceptibility was evaluated in 84 isolates with OXA-48 and KPC carbapenemase activity. Both BMD and disk diffusion methods revealed that 95.2% of the isolates were sensitive to CZA; whereas, 4 (4.76%) isolates were resistant to CZA. Among colistin resistant isolates, 96.5% (n = 80) of them were susceptible to CZA. Our study demonstrated high in vitro efficacy of CZA in Enterobacterales isolates producing OXA-48 carbapenemase. High susceptibility rates against colistin resistant isolates which generally are also pan drug resistant, makes CZA a promising therapeutic choice for difficult-to-treat infections. Due to its high correlation with the BMD, disk diffusion method is a suitable and more practical method in detecting CZA in vitro activity.

-Lübnan’da çok ilaca dirençli gram negatiflerin durumu ve antibiyotik yönetimi

-Karbapenem dirençli Enterobacteriaceae, *Pseudomonas aeruginosa* ve *Acinetobacter baumannii* enfeksiyonlarında güncel tedavi yaklaşımı ve klavuzlar

-Ampirik tedavi yaklaşımı ve ampirik tedaviyi değiştirme koşulları

-De-eskalasyon

-Duyarlılık test sonuçlarına göre hedeflenmiş tedavi yaklaşımı